A MOUNT SINAI HOSPITAL
MONOGRAPH

CENTRAL FOOD TECHNOLOGICAL RESEARCH INSTITUTE * MYSORE *
29.9.58
LIBRARY

CFTRI-MYSORE
3923
Malabsorption sy.

45.3

8/8/18

RMS

A MOUNT SINAI HOSPITAL MONOGRAPH ON

The Malabsorption Syndrome

EDITOR

DAVID ADLERSBERG, M.D.

Associate Attending Physician for Metabolic Diseases,
The Mount Sinai Hospital, New York;
Assistant Clinical Professor of Medicine,
College of Physicians and Surgeons, Columbia University, New York

CONTRIBUTIONS TO THE SYMPOSIUM

BY MEMBERS OF THE STAFF OF THE MOUNT SINAI HOSPITAL, NEW YORK

David Adlersberg
Elaine T. Bossak
Henry Colcher
David A. Dreiling
Joan Eliasoph
Solomon Estren
Joel Hartley
Hilliard W. Himes
Henry D. Janowitz
Edgar Kogan
Burton I. Korelitz
Richard M. Marshak
Sanford Oxenhorn
Adolfo Schapira
Walter Sencer
Ch'un-I Wang
Bernard S. Wolf

GUEST CONTRIBUTORS

W. Trevor Cooke
Margot Shiner

CENTRAL FOOD TECHNOLOGICAL RESEARCH INSTITUTE, * MYSORE. *
LIBRARY

GRUNE & STRATTON
NEW YORK

1957
LONDON

This Symposium has been prepared for simultaneous distribution as the May–June 1957 issue of the Journal of the Mt. Sinai Hospital and its contents are copyright as such. All rights reserved.

3923.
L,25;4'p
N57.

CFTRI-MYSORE
3923
Malabsorption sy..

SYMPOSIUM

The Malabsorption Syndrome

CONTENTS

FOREWORD. *Henry L. Bockus* 1

INTRODUCTION. *David Adlersberg* 3

THE PHYSIOLOGY OF INTESTINAL ABSORPTION. *Burton I. Korelitz and Henry D. Janowitz* 7

DISTURBANCES IN PROTEIN AND LIPID METABOLISM. *David Adlersberg, Ch'un-I Wang and Elaine T. Bossak* 32

WATER AND ELECTROLYTE UPSETS. *W. Trevor Cooke* 47

ALTERATIONS IN VITAMIN B_{12} ABSORPTION. *Sanford Oxenhorn, Solomon Estren and David Adlersberg* 58

PANCREATIC SECRETION STUDIES. *David A. Dreiling* 69

PATHOLOGIC STUDIES. *Hilliard W. Himes and David Adlersberg* 77

BIOPSIES OF THE SMALL INTESTINE. *Margot Shiner* 99

CLINICAL ASPECTS. *Elaine T. Bossak, Ch'un-I Wang and David Adlersberg* 112

BLOOD AND BONE MARROW MANIFESTATIONS. *Solomon Estren* 130

HEMORRHAGIC MANIFESTATIONS. *Ch'un-I Wang and Elaine T. Bossak* 143

NEUROLOGIC MANIFESTATIONS. *Walter Sencer* 157

OSSEOUS CHANGES AND FRACTURES. *Joel Hartley* 172

ROENTGEN FINDINGS. *Richard M. Marshak, Bernard S. Wolf and Joan Eliasoph* 188

MANAGEMENT. *Henry Colcher and David Adlersberg* 206

MALABSORPTION FOLLOWING EXTENSIVE SMALL BOWEL RESECTION. *Edgar Kogan, Adolfo Schapira, Henry D. Janowitz and David Adlersberg* 225

INDEX 251

FOREWORD

The publication of this symposium on the malabsorption syndrome is timely. The syndrome occurring in the adult has been variously termed "nontropical sprue" (Homes and Starr) and "idiopathic steatorrhea" (Bennett, Hunter and Vaughn). Recently and more appropriately the label "idiopathic malabsorption syndrome" has been attached to it. Most observers feel that there is a close association between the adult affection and the celiac syndrome of childhood. There are some who would not agree with the editor that tropical sprue is but a variant of the so-called idiopathic malabsorption syndrome. Certainly the tropical variety tends more often to be reversible, so that the absorption defect may be only temporary. It seems to be associated more often with a more severe anemia with a greater tendency toward glossitis and stomatitis and with more severe diarrhea. Tropical sprue responds more consistently to the administration of folic acid. However, as Dr. Adlersberg has stated, everyone with tropical sprue or the idiopathic malabsorption syndrome may have the same basic metabolic defect. Perhaps many of those with tropical sprue may have the defect to a lesser extent, i.e., the abnormality remaining occult until the occurrence of a precipitating factor, such as long-standing undernutrition or chronic infection or infestation. It may very well be that the so-called metabolic defect is greater among persons in the colder climates and the trigger mechanism may not need to be so striking.

This syndrome has attracted a good deal of attention recently because of an attempt to define more clearly the underlying defect, and it is for this reason that many observers have become more interested in differences that exist in the syndrome as it appears in various parts of the world. More important, newer technics have appeared for the differentiation of the anemias that occur in association with the syndrome. Furthermore, some of the newer absorption tests employing labeled fat and radioactive B_{12} have great promise. These more recent diagnostic methods will certainly facilitate the differential diagnosis between primary pernicious anemia and the primary malabsorption syndrome. The labeled fat tests will unquestionably prove helpful in the differential diagnosis of idiopathic steatorrhea from the steatorrhea of pancreatic insufficiency. The popularity of the gluten-free diet and the increased utilization of ACTH and adrenal steroids has added a good deal to our therapeutic armamentarium and increased our fundamental knowledge of the affection.

The contributions from our British colleagues record experiences which they are particularly well qualified to relate, i. e., electrolyte disorders (Cooke) and histologic studies based upon material obtained by jejunal biopsies (Shiner).

All of these facets and many others are covered in this monograph. It is fitting that the group from Mt. Sinai should record their experience in this manner. They have had a large contact with the spruelike state and are recording at this time an extensive follow-up on ninety-four patients. The long association together of this group of workers who have participated in the study of this syndrome adds considerably to its value. Group efforts of this type are often rewarding because of the opportunity for frequent conferences and for exchange of ideas on the same group of patients.

This monograph should serve a valuable purpose to those interested in the research and in the clinical aspects of the malabsorption syndrome. Factual and theoretical data have been well summarized. I congratulate Doctor Adlersberg for his diligent and understanding devotion to the study of malabsorption through the years.

HENRY L. BOCKUS, M.D.

University of Pennsylvania
Graduate School of Medicine
Philadelphia, May 1957

INTRODUCTION

A classical description of the clinical entity presented in this symposium, the malabsorption syndrome, reads as follows:

> "Wherefore they have flatulence of the stomach, continued eructations, or a bad smell; but if these pass downwards, the bowels rumble, evacuations are flatulent, thick, fluid or clayey, along with the phantasy, as if a fluid were passing through them; heavy pain of the stomach now and then, as if from a puncture; the patient emaciated and atrophied, pale, feeble, incapable of performing any of his accustomed works. But if he attempts to walk, the limbs fail; the veins in the temples are prominent, for owing to wasting, the temples are hollow; but also over all the body the veins are enlarged, for not only does the disease not digest properly, but it does not even distribute that portion in which the digestion had commenced for the support of the body; it appears to me, therefore, to be an affection, not only of the digestion, but also of the distribution."

Aretaeus the Cappadocian (second century A.D.) is credited with the above earliest description of this disorder (1). Hanes believes that "although it is admittedly difficult to identify ancient description with modern disease entities, yet one familiar with the sprue syndrome will hardly fail to recognize the lineaments of sprue in Aretaeus's graphic portrayal" (2). Paraphrasing Aretaeus' last sentence we like to consider him a precursor of those who believe that the malabsorption syndrome is an affection "not only of the digestion but also of the metabolism."

After an interval of many centuries Samuel Gee presented towards the end of the 19th century his studies "On the Coeliac Affection" (3).

> "There is a kind of chronic indigestion which is met with in persons of all ages, yet is especially apt to affect children between one and five years old. Signs of the disease are yielded by the faeces, being loose, not formed, but not watery; more bulky than the food eaten would seem to account for; pale in colour as if devoid of bile; yeasty, frothy, an appearance due to fermentation; stinking, stench, often very great, the food having undergone putrefaction rather than concoction. . . ."
>
> "The causes of the disease are obscure. Children who suffer from it are not all weak in constitution. Errors in diet may perhaps be a cause, but what errors. . . ."
>
> "Naked-eye examination of dead bodies throws no light upon the nature of the coeliac affection; nothing unnatural can be seen in the stomach, intestines, or other digestive organs. . . ."
>
> "The patient wastes more in the limbs than in the face, which often remains plump until death is nigh. In the limbs emaciation is at first more apparent to hand than to eye, the flesh feeling soft and flabby . . . the belly is mostly soft, doughy, and inelastic; sometimes distended and rather tight. Wind may be troublesome and very foetid. Appetite for for food differs in different cases, being good, or ravenous, or bad. . . ."
>
> "When recovery is incomplete, the illness drags on for years; the patient getting better on the whole, but being very subject to relapses of his complaint. While the disease is active the children cease to grow; even when it tends slowly to recovery, they are left frail and stunted. . . ."

This contribution of Samuel Gee is considered "a classic, and very little has been added to Gee's clinical and pathologic observations by subsequent writers" (2). It is of interest that in Gee's opinion children and adults were similarly affected. Gee was probably the first author to express, as early as 1888, the view that celiac disease in children is analogous to sprue in adults.

During this century and especially in the last two decades there has been increasing interest in the clinical manifestations as well as in laboratory and autopsy findings in the malabsorption syndrome. Important information has been contributed in various parts of the world, especially in Britain, Scandinavia, the United States and other American countries, as may be seen from the extensive references appended to the subsequent articles of the symposium. Increasing evidence supports the concept that tropical sprue, non-tropical sprue, often referred to as the idiopathic steatorrhea syndrome, and celiac disease of childhood, are clinical varieties of the same metabolic disorder, primary or idiopathic malabsorption syndrome. Nevertheless some authorities in the field (4) are of the opinion that these conditions are "outwardly similar but inwardly dissimilar". A critical analysis reveals however that these dissimilarities, interesting as they may be (5), are too superficial to warrant definition of tropical and non-tropical sprue and of celiac disease as independent clinical entities. Celiac disease as seen today appears to be a milder variety of the malabsorption syndrome occurring in children. None of the clinical features are limited to this form of the malabsorption syndrome. The complications of celiac disease such as retardation of growth and rickets are fully explained by the onset of the symptoms of the disorder in childhood. On the other hand similar complications may be seen in adults with sprue, such as osteomalacia with various degrees of bone changes (6). The response of celiac disease to gluten-free diets again is not specific since adults with malabsorption syndrome, especially the milder forms, also may respond satisfactorily.

Although "cure" was more frequently observed in celiac disease and in the tropical variety of sprue than in non-tropical sprue, recent extensive studies revealed persistence of the metabolic abnormality and radiologic small bowel signs in seemingly asymptomatic celiacs (7) and in patients with "cured" tropical sprue (8).

The high familial incidence of celiac disease is well documented (9). Students of tropical sprue frequently report the occurrence of the disease in several members of the same family ("sprue houses") (10). In non-tropical sprue familial occurrence is no rarity according to our own observations and those of many others (10–12).

In the broader view of today primary malabsorption syndrome may be defined as a genetically transmitted metabolic disorder. Intestinal malabsorption and hematologic changes are the main facets of clinical interest. There are in addition many other metabolic abnormalities not necessarily related to the absorptive and hematic difficulties as will be demonstrated in some of the following papers. Profound disturbances in genetically controlled, enzymatic chain reactions apparently affect intestinal absorption as well as the metabolism of proteins, lipids, electrolytes and water. Despite the genetic anlage, the malabsorption syndrome may become manifest at various periods of life. In analogy to other inherited errors of metabolism, e.g., diabetes, malabsorption syndrome may become clinically manifest in infancy or childhood as celiac disease, or later in life as tropical or non-tropical sprue. Actually a number of our patients with non-tropical sprue presented celiac disease in childhood. The stress of tropical climates, preceding tropical or non-tropical infections, malnutrition and probably wheat or rye gluten are important precipitating factors or triggering mechanisms. These factors will convert a predisposed person with "latent malabsorption syndrome" into a patient with "manifest malabsorption syndrome".

Primary malabsorption syndrome must be strictly separated from secondary malabsorption syndromes. In primary malabsorption syndrome there are no clinical roentgenologic or post-mortem evidences of gross organic disease entities involving the gastrointestinal tract, pancreas or liver. In secondary malabsorption syndromes gross pathologic alterations may be encountered in the gastrointestinal tract, such as extensive lymphosarcoma or amyloidosis of the small bowel and/or the mesenteric lymph glands, intestinal lipodystrophy or certain forms of jejunoileitis; or after-effects of surgical procedures, such as extensive resection or exclusion of parts of the small bowel; or pathologic conditions in the pancreas, such as pancreatitis or carcinoma; or changes in the liver or biliary tree, such as mechanical biliary obstruction. Secondary malabsorption syndromes mimic the primary form but can be differentiated on clinical grounds, by the use of laboratory procedures and eventually by biopsy or autopsy.

The symposium presented in this volume is primarily concerned with primary or idiopathic malabsorption syndrome. The physiologic aspects of intestinal absorption are presented first. Abnormalities in the metabolism of proteins and lipids, of water and electrolytes are then discussed as well as disturbances in the intestinal uptake of vitamin B12 and in pancreatic enzymes. The subsequent papers deal with pathologic findings based on autopsy and biopsy studies. The presentation of the clinical aspects is based on analysis of a selected group of 94 patients observed over an average period of 5.2 years at The Mount Sinai Hospital. Special articles are devoted to the changes in blood and bone marrow, to hemorrhagic manifestations, to neurologic and bone complications. The roentgenologic appearance of the small bowel is discussed extensively. The management of malabsorption syndrome is presented with special reference to dietary management, including gluten-free diet, and steroid therapy. The last paper is devoted to an important secondary malabsorption syndrome: the diagnostic and therapeutic problems encountered in patients with extensive resection or exclusion of the small bowel. It was impossible to include all aspects of malabsorption syndrome in the symposium, e.g., there is no comprehensive discussion of celiac disease.

The symposium presents many recent advances in our knowledge of malabsorption syndrome. It is apparent, however, that there are considerable gaps in our knowledge particularly with regard to the basic mechanisms responsible for the disorder. This presents a challenge to all those who are actively interested in this baffling clinical entity.

The Editor is very deeply obliged to his colleagues at The Mount Sinai Hospital, contributors to this symposium, for their unlimited and enthusiastic interest in preparation of the papers. He wishes to express his appreciation to Dr. Cooke in Birmingham and Dr. Shiner in London, the two "extramural" contributors to this symposium, for their willingness to participate in this venture.

The Mount Sinai Hospital
New York, March 1957

DAVID ADLERSBERG, M.D.
Editor

REFERENCES

1. *Aretaues the Cappadocian: Extant Works.* Edited and translated by FRANCIS ADAMS, London. Sydenham Soc. 1856, p. 350.
2. HANES, F. M.: *Sprue, in Tice's Practice of Medicine, Hagerstown, Md.* W. F. Prior, Inc. 1943, Vol. 4, p. 171.
3. GEE, S.: On the Coeliac Affection. S. Barthol. Hosp. Report., 24: 17, 1888.
4. MANSON-BAHR, P.: *The Dysenteric Disorders.* Baltimore, 1943. The Williams & Wilkins Co.
5. BOSSAK, E. T., WANG, C. I., AND ADLERSBERG, D.: Clinical Aspects of the Malabsorption Syndrome (Idiopathic Sprue). Observations in 94 Patients. This volume, page 112.
6. HARTLEY, J.: Osseous Changes and Fractures in Malabsorption Syndrome. This volume, page 172.
7. DI SANT' AGNESE, P. A.: Idiopathic Celiac Disease II. Course and Prognosis. Pediatrics, 11: 224, 1953.
8. GARDNER, F.: A Malabsorption Syndrome in Military Personnel in Puerto Rico. A.M.A., Arch. Int. Med., 98: 44, 1956.
9. THOMPSON, M. W.: Heredity, Maternal Age, and Birth Order in the Etiology of Celiac Disease. Am. J. Human Genetics, 3: 159, 1951.
10. THAYSEN, T. E. HESS: Non-tropical Sprue, Copenhagen, 1932, Levin & Munksgaard.
11. DAVIDSON, L. S. P., AND FOUNTAIN, J. R.: Incidence of the Sprue Syndrome with some Observations on the Natural History, Brit. Med. J., 1: 1157, 1950.
12. COOKE, W. T., PEENEY, A. L. P., AND HAWKINS, C. F.: Symptoms, Signs and Diagnostic Features of Idiopathic Steatorrhea. Quart. J. Med., N.S. 22: 59, 1953.

THE PHYSIOLOGY OF INTESTINAL ABSORPTION

BURTON I. KORELITZ, M.D.
AND
HENRY D. JANOWITZ, M.D.

New York, N. Y.

It is both appropriate and logical to discuss the physiology of normal intestinal absorption in a symposium devoted to the clinical syndromes of malabsorption. It is doubtful however whether the incomplete state of our knowledge of these processes can at present shed much light on the fundamental defects of the clinical states. Indeed there is reason to believe that unraveling of the pathophysiology of absorption will rather facilitate our understanding of the normal processes. Be that as it may, it is the function of this review to summarize some of the current concepts and hypotheses of absorption from the small intestine.

For this purpose, *absorption* is the process by which materials are transferred from the lumen of the gut across the intestinal mucous membrane to blood and lymph vessels: the transport of nutriments from the exterior milieu to the interior milieu; a process which Fisher and Parsons have neatly labelled *translocation* (1).

In any generally comprehensive schema intestinal absorption represents a special example of the permeability of natural membranes. While some progress has been made towards such comprehensive generalization, the details of which may be found in the monograph of Davson and Danielli (2), the intestinal membrane is such a complex tissue that few overall generalizations can be made with safety at present.

In the regulation of absorption it should be remembered that when materials are presented to the normal intestinal membrane in appropriate form, these are absorbed independent of bodily requirements. There is only one important exception to this statement. Iron appears to be the only nutritive material whose absorption is regulated in keeping with bodily needs (see below). For all other substances it is *intake* and thus hunger and appetite which regulate the quantities absorbed.

Digestion as related to absorption. The main components of the diet are complex, large molecules which do not easily penetrate the intestinal membrane, with few exceptions, and if they do penetrate are poorly utilized. To facilitate absorption, these dietary substances of high molecular weight are broken down to smaller ones which are water-soluble, diffusible, or have active groups by a series of enzymic catalyzed hydrolyses. This preliminary process is properly designated as *digestion* and falls outside the scope of the present review. In the case of fat, however, the role of the digestive secretions, especially bile salts and the lipolytic enzymes, are so intimately concerned with the problem of absorption that some consideration of fat digestion must be included in the discussion of fat absorp-

From the Department of Medicine, The Mount Sinai Hospital, New York City.

tion. Indeed, one of the fundamental not yet completely resolved problems in the field is the extent to which fat, especially triglyceride fat, must be split prior to absorption.

The structure of the membrane. Substances moving across membranes, and the intestinal membrane specifically, fall in the main into two groups: (1) those which move by diffusion according to their concentration gradients, moving from regions of higher to lower concentration, so called passive movement and (2) those able to move against a concentration gradient, a process which requires the expenditure of energy, so called active transport or selective absorption. Further, a substance (such as glucose) may exhibit both kinds of behavior. The cellular mechanisms responsible for the active absorption or transfer of the second group are almost completely unknown, although they are obviously connected with the fundamental structure of the absorbing membrane.

In man, as in most animal species, the main cell of the intestinal epithelium is a cylindrical cell (22 to 26μ by 6 to 9μ). Interspaced among these is a mucous secreting cell, the goblet cell. It is not clear whether the mucous secretion forms a continuous surface layer, as is believed to be the case in the stomach.

The free border of the intestinal epithelium, since it is the focal point of transfer, has been the object of histological study for more than a century and only recently is its nature beginning to be clarified. All workers have recognized a striated border at the free surface of the intestinal cell, but opinion has been divided between ascribing a pore-canal system to it or a rod-like tubular structure.

The most careful studies of this border by the light microscope appeared to favor the canal theory (3). However, more recent analyses with the use of the electron microscope have demonstrated that the striated border on the free surface of the absorptive cell is composed of a palisade of columnar rodlets, with blunt rounded tips, closely packed together. The striking electron micrographs of Granger and Baker (4) deserve careful attention from all interested in the fundamental aspects of the process of absorption. These authors have estimated that a single columnar cell must bear nearly 3,000 such rodlike processes, and a square millimeter of intestinal surface some 200 million. Their presence appears to increase the absorptive surface of the gut about 30 fold.

The more recent studies of Sjöstrand and Zetterquist (5) with ultra thin sectioning and electronmicroscopy have confirmed and clarified the nature of the the rod-like processes of the epithelial border. This functional increase in surface area is consistent with the other anatomical characteristics of the small bowel: its great length, the mucous folds (Kerkring folds or *valvulae conniventes*) and most strikingly the finger-like reduplication of the mucosa, the intestinal villi. In man it has been estimated that there are 18 to 40 villi per square millimeter of intestinal surface, and an increase of surface area due to the villi of about 7 fold.

Movement of the villi following feeding seems to be clearly established, and there is fragmentary evidence that a humoral mechanism may be involved as well as a local neuro-mechanical one. The significance of this villous movement in the process of absorption however is far from established. An important "pumping" role has been ascribed by Verzar to villous contraction in emptying the central lacteal of absorbed fat and will be touched upon again in the section on fat absorption.

Methods of research. Progress in revealing the cellular mechanisms involved in absorption has been hindered by the lack of truly physiological methods of investigation. Experiments which involve concomitant studies of intestinal contents and the blood and lymph represent an end result of digestion, translocation, transport and intestinal utilization rather than absorption alone.

Prior to 1925 most of the available information was derived from the study of animals with permanent intestinal fistulas, ligated loops of intestine, by weighing of different parts of the body or by study of histological preparations of mucosa. Then Cori (6) introduced the method of feeding a known amount of substance by stomach tube to rats and killing them after a given period. The amount of the substance remaining in the intestine was then determined quantitatively. This method represented a great advancement and was a source of reliable information.

In 1934 Miller and Abbott (7) first described their double-lumened, single-ballooned tube which was utilized in the study of human absorption. Two years later these same investigators (8) overcame many technical difficulties by the development of a triple-lumened tube with two balloons. These tubes offered a satisfactory method of controlling the site of absorption and length of segment, and, by the introduction of known concentrations and recovery, aided the study of osmotic relationships, motility and their affect on absorption. Others (9, 10, 11, 12, 13, 14, 15) later found modifications of this method of investigation to be fruitful.

Technical methods for research in absorption were then virtually at a standstill until 1949, when Fisher and Parsons (1) described the first *in vitro* apparatus. This consisted of the establishment of two complete circulations, an inner and an outer. The two circulations were separated by a length of animal small intestine such that the inner circulation (mucosal) was completed by the lumen of the intestine, and the outer circulation (serosal) flowed around the intestine. Transfer of a substance from the inner to the outer circulation could take place only by way of the intestinal wall. The success of this apparatus is partially dependent on the feature that the mucosal cells are minimally deprived of oxygen. The structure of the apparatus is such that the physical factors (temperature, pH, solute concentration and concentration gradient) could be controlled.

Other forms of *in vitro* apparatus (16, 17), methods (18), and modifications of these (19, 20, 21, 22, 23) soon followed. The introduction of radio-active isotopes in conjunction with both *in vivo* and *in vitro* studies has been revealing (21, 24). It is from these sources that knowledge of the actual mechanisms, particularly of glucose and amino acid absorption, is slowly evolving.

Progress in the study of fat absorption has been considerably advanced by several technical methods: (1) the introduction of a technique for collecting lymph from the intestinal or thoracic duct in unanesthetized animals by Bollman, Cain and Grindley (25); (2) the development of analytic methods for the estimation of glyceride mixtures and isolation and separation of fatty acids and phospholipids and (3) the use of isotopically labelled fatty acids, glycerol and glycerides.

FAT ABSORPTION

The mechanism of intestinal fat absorption, an understanding of which is probably central for a complete analysis of the malabsorption syndromes, is a complex as yet incompletely resolved problem, about which much controversy has been collected during the last fifty years. We intend merely to indicate some of the strands of this tangled knot.

Site of fat absorption. From histological studies it has been demonstrated that fat can be absorbed at all levels of the small intestine. What is not known is the site of preferential or maximal absorption. Recently some experimental evidence has suggested that the distal small bowel is more important for fat absorption than the proximal. Kremens and co-authors (26) have demonstrated in the dog that sacrifice of the proximal 50 per cent of the small intestine could be tolerated, but that removal of the distal 50 per cent led to a profound interference with fat absorption. Studies in the rat have indicated that such may be the case in this species as well, the third quarter of the small intestine being most important for fat absorption (27).

The intraluminal phase. It seems clear that neutral fat can be absorbed only if there is hepatic secretion of bile salts and pancreatic secretion of lipase. The bile salts, glyco- and tauro-cholate, appear to have no lipolytic activity themselves but act by emulsifying fat prior to lipase action, thus increasing enzyme substrate contact. Recent studies have shown that these salts function as do other effective detergents by a fat-attracting portion (CH_2 and ethyl groups) and a water-attracting portion (OH, SO_3 or COOH groups). This arrangement results in the formation of micelles in which the hydrocarbon fat-attracting portion lies in the center, and the polar (OH, SO_3, or COOH) portions on the outside in contact with the surrounding aqueous solution (27A).

In the classical or lipolytic view of fat absorption, promulgated by Pflüger, triglyceride fat in the presence of bile salts and lipase is split completely to fatty acids and glycerol. These products, absorbed in water-soluble form, are then resynthesized in the intestinal cell to neutral fat which enters the lymphatic vessels of the gut and ultimately reaches the venous circulation by way of the thoracic duct. The bile salts return to the liver by way of the portal vein. A great deal of the evidence for this view was derived from the classical observations of Munk and Rosenstein in 1891 on a patient with a lymph fistula of the thigh. A high proportion of fat fed to this patient could be recovered from the fistula, mostly in the form of neutral fat, after ingestion as triglyceride, free fatty acid or amyl esters of long-chain fatty acids.

The lipolytic theory was refined by the studies of Verzar and his collaborators, summarized in their monograph "Absorption from the Intestine" (28). The absorption of fatty acids would be accomplished by the formation of water-soluble complexes with the conjugated bile acids (glycocholic and taurocholic acid) at the slightly acidic pH of the upper small gut. This group of investigators also put forward the concept that the synthesis of neutral fat from the absorbed glycerol and fatty acids proceeds through an intermediate phosphatide step, under the control of the adrenal cortex. This step involving phosphorylation was believed to be inhibited by high concentrations of phlorhizin and by iodoacetic acid. But the general outlines of the lipolytic hypothesis were essentially unaltered.

A vigorous experimental critique of this theory has been advanced by A. C. Frazer since 1934, to which the term "partition theory" has attached, although this theory too has undergone modification at its author's hand (29). Frazer interpreted his evidence to mean that there are two pathways for fat absorption: (1) highly emulsified particulate neutral fat can be absorbed directly through the intestinal cell to enter the lymph, and (2) fatty acids (derived from lipolysis) enter the portal circulation to be deposited in the liver. A series of studies on the emulsifying action of monoglycerides in the presence of bile salts and on the absorption of highly emulsified paraffin in glyceride mixtures were interpreted as supporting the direct absorption of unsplit fat at particle sizes 0.5μ or smaller.

Recent studies involving newer methods for collecting mesenteric lymph and using isotopically labelled fats and fatty acids have diminished the force of Frazer's partition theory, at least as originally formulated. Bloom and coauthors (30) showed that C^{14} labelled palmitic acid could be recovered to the extent of 92 per cent in lymph, and similar results have been obtained for stearic, palmitic and pentadecanoic acids. These results, which were interpreted as being inconsistent with the partition hypothesis, have been critized since glyceride vehicles were used for the fatty acid feedings. However, experiments in which free fatty acids were fed have yielded substantially the same results, the only difference being the slower rate of absorption of the free fatty acids as compared with the glycerides. This type of evidence is extremely strong support for the lipolytic theory, and the resynthesis of neutral fat by the intestinal mucosa.

That several mechanisms may be operative however is indicated by two important lines of evidence: (1) Frazer has consistently stressed the point that complete hydrolysis of glycerides to fatty acids and glycerol before absorption is not an obligatory step. Reiser and co-workers (31), and others, recently have shown that some portion (50 per cent or more) of absorbed fat has been hydrolyzed down to monoglycerides but not to smaller molecules. This certainly would seem to indicate that lipolysis need not be complete. This fat, whatever its degree of lipolysis before absorption, is recovered as resynthesized triglyceride fat in the lymph. In this context it is of interest that recent evidence indicates that glycerol liberated during lipolysis is absorbed via the portal system, and utilized for the synthesis of triglycerides or phospholipids in the intestinal cells or contents to only an extremely small extent. (2) Studies in several laboratories have shown that there is a differential partition between the chyle and portal blood as between long- and short-chain fatty acids (2)—fatty acids of 10 carbon atoms or less are absorbed by the portal vein while the longer-chained fatty acids of dietary fat are absorbed by the lymphatics. Thus Bloom and others feeding C^{14}-labelled fatty acids to rats found that 84 to 85 per cent of stearic acid, 59 to 82 per cent of myristic acid, 15 to 55 per cent of lauric acid, and only 7 to 19 per cent of decanoic acid was recovered in the lymph (32). It is of interest in this context that, of the common dietary lipids, only cows' milk is relatively abundant in shorter-chain fatty acids.

In conclusion, although neutral fat need not be hydrolyzed completely before absorption, the major portion of dietary fat is split to monoglycerides, fatty acids and glycerol in the intestinal lumen in the presence of bile salts and pancreatic lipase. The long-chain fatty acids are absorbed and enter the mesenteric lymph as triglycerides and the short-chain fatty acids enter the portal system as such, along with glycerol.

Cellular mechanisms of fat translocation. Within 1½ to 2 hours after a fatty meal in animals, sudanophilic material can be recognized histologically within the intestinal cell. Whether neutral fat or fatty acids is fed, lipoid material can be seen in the striated lumenal border of the cell. The mechanism of this passage is not clearly understood at present. At the pH of the intestine (6.7 to 6.8) the fatty acids are probably presented to the membrane in several forms: ionized molecules (RCO_2), neutral molecules (RCO_2H), as complexes with bile salts and perhaps as soaps (alkaline salts). Pflüger's original concept that absorption as soaps was the most important mechanism fell into disrepute with the demonstration of the actual pH of the intestine on the acid side of pH 7; yet recent studies by Schmidt-Nelson have indicated that as much as 10 to 25 per cent of the fatty acids could exist as soaps at this pH. The importance of soaps in the problem of calcium absorption will be touched upon below.

Most theories of cell membranes postulate a lipoid layer at the surface and these fatty substances could thus easily diffuse into the membrane. What is difficult to explain is their diffusion out of the membrane into the aqueous interior of the cell. Verzar (28) believed that an active process of transport is involved since phlorhizin, which is supposed to inhibit phosphorylation, and monoiodoacetic acid, which inhibits glycolysis, both inhibit the transport of fat across the mucosal cell. In this formulation the fats are transformed into phospholipids in the course of this transfer. It is of considerable interest in connection with the therapeutic aspects of this symposium that Verzar and his colleagues ascribe a regulating function to the adrenal cortex over this stage. In adrenalectomized rats there was a marked impairment of fat absorption. From histologic evidence they concluded that the entrance of fatty acids into the cell continued, but that the resynthesis of fatty acids was inhibited in the adrenalectomized animals. Surprisingly, with the cortical extract of Swingle and Pfiffner (1935) they were able to correct this defect.

Mucosal phospholipid formation during absorption. When labelled stearic acid was fed to rats either as glyceride, free acid, or as cholesterol ester, about 10 per cent of the total lymph fatty acid was recovered in the form of phospholipid (33). There is also available evidence that during absorption of fat, the amount of neutral fat and fatty acid of the gut increases, but the amount of phospholipids remains relatively constant. There are changes, however, in the quantitative fatty acid composition of the intestinal phospholipid depending on the fat being absorbed. This led Sinclair in 1929 to postulate that phospholipids were involved as intermediates in the resynthesis of triglycerides and in the intracellular transport of fatty acids (34). Studies of labelled phosphate have also indicated an increased turnover of the phosphorus portion of phospholipids of the intestinal wall during fat absorption. However, there has been much difficulty in accounting quantitatively for the conversion of all fat to phospholipid during transport, but Bergstrom and Borgstrom point out that it is the phospholipid of the epithelial cell and not of the whole gut which must be involved in this process (35).

The inhibition by phlorhizin of fat absorption is ascribed by some workers not to a specific action on phosphorylation but to inhibition of a variety of enzymatic processes which couple oxidation to phosphorylation in the generation of high-energy phosphate bonds.

In conclusion, the hypothesis that every molecule of fat passes through a phospholipid stage in getting from the lumenal to the lacteal border of the intestinal cell remains an interesting but unproved one.

The fine fat particles, having accomplished their passage across the intestinal cell, pass into the lymphatics of the villus. Frazer (29) has stated that this is in accordance with the behaviour of other negatively charged particles which when introduced into the tissues tend to pass into lymphatics rather than blood capillaries. From histological evidence Verzar believes that the muscular contraction of the villi produces a pumping action which tends to empty the central lymph channel and thus move the chyle on. This remains controversial at present. Wells and Johnson (57) deny that shortening of the villi empties the lacteals.

The absorption of other related lipid substances. In the absorption of sterols from the gut specific mechanisms appear to be operative. Cholesterol in the presence of bile salts is readily absorbed. However allocholesterol (an isomer of cholesterol), the four isomers of dihydrocholesterol, coprosterol (a reduction product of cholesterol produced by intestinal bacteria), cholestanol (a tissue reduction product of cholesterol secreted in limited amounts into the gut), as well as phytosterols of plant origin are poorly if at all absorbed. Since all these substances are emulsified by bile, and many diffuse through artificial membranes, it appears that there is marked specificity of the intestinal transport system. Verzar believes that esterification of cholesterol is an essential step in absorption, and that other sterols may not be absorbed because of the absence of appropriate enzyme systems. Under ordinary circumstances the cholesterol presented to the gut is almost entirely free cholesterol, yet a considerable portion of that recovered in the thoracic lymph is in the form of esters. Absorption of cholesterol appears to involve some esterification, and is enhanced by fat as well as bile in the digestive mixture.

In view of the lymphatic transportation of cholesterol, it is puzzling that recent studies appear to indicate that cortisone, hydrocortone and testosterone (not too dissimilar in basic structure from cholesterol) appear to be absorbed from the intestine by the portal venous route. Lecithin appears to be broken down to its constituents which are absorbed as such.

The enterohepatic circulation of bile salts has been discussed already. It is of interest that glycocholates and taurocholates are better absorbed from the jejunum and ileum than from the duodenum.

The absorption of substances dependent on fat absorption, or related to fat absorp-

tion. In this group of substances are the fat-soluble vitamins: A, D, E and K. Vitamin D and its provitamin ergosterol are sterols, while the others are included here because of their solubility in fat and lipid solvents.

1. *Vitamin D*. Although almost all vegetable sterols pass through the intestinal membrane in limited quantities, vitamin D is an exception. The provitamin ergosterol was shown by Schoenheimer not to be absorbed until it is activated by ultraviolet radiation and becomes vitamin D_2 (calciferol). Like other sterols vitamin D requires bile and apparently a certain amount of fat. The exact mechanism of vitamin D absorption is unknown.

2. *Vitamin A*. The absorption of vitamin A and its provitamins, the carotenes, since they are fat-soluble, is determined in great part by the factors determining the absorption of lipids, although it is believed that preformed A and the carotenes can possibly be absorbed without the presence of bile salts. Failure to absorb fat from the gut will lead to a loss of carotenes and vitamin A in the fecal fat, and emulsification of lipid mixtures will improve vitamin A absorption.

3. *Vitamin E*. Although it is not established at present that the tocopherols are essential for man, vitamin E absorption is linked to lipid absorption because of its solubility.

4. *Vitamin K*. Because of its solubility in lipids, vitamin K also is governed by factors which influence the intestinal absorption of fat. Natural K vitamins require bile salts for this absorption, while synthetic water-soluble compounds with vitamin K activity can be absorbed without bile salts.

In general the immediate cellular mechanisms of transfer of these fat-soluble vitamins are unknown. Failure of fat absorption leads to interference in the absorption of these substances presumably because of their solubility in the fats.

Calcium absorption. The intestinal absorption of calcium is also discussed at this point not because the cellular mechanisms of calcium absorption are related to the cellular mechanisms of fat absorption but because disturbances in fat absorption lead to interference with calcium absorption. The major portion of dietary calcium is ingested as calcium phosphate which is difficultly soluble at the pH of the intestine. It is this solubility of calcium which is critical for its absorption since as far as is known only ionic calcium crosses the intestinal cell. A number of factors influence absorption by virtue of their effect on the solubility of calcium salts within the intestinal lumen: a high ratio of phosphate to calcium in the diet will render calcium less soluble, the phytic acid of cereals form insoluble calcium phytate, oxalic acid has a similar effect, while citrates favor absorption by lowering intestinal pH and forming calcium citrate which is relatively soluble.

Protein appears to favor calcium transport presumably due to soluble calcium compounds formed with the amino acids produced by protein digestion. Under conditions of normal fat digestion and absorption the proportion of fat and calcium in the diet appears to have little reciprocal effect on each other. When fat digestion and absorption are defective, calcium forms insoluble calcium soaps with fatty acids and is lost in the stool. In addition, the loss of vitamin D in the steatorrhea also contributes to the inefficiency of calcium absorption.

It has been conclusively established that vitamin D increases calcium absorption from the intestine but the mechanisms are not known. In rats studied with radio-active calcium, absorption occurred during the first 2 to 4 hours after administration, uninfluenced by vitamin D, but after that time vitamin D was necessary for further absorption. Vitamin D causes lowering of intestinal pH, but it is not known whether the vitamin causes a depletion of base in the intestine directly, or whether this is secondary to the increased calcium absorption itself lowering intestinal base.

CARBOHYDRATE ABSORPTION

There is probably more available information on the absorption of sugars than of protein or fats, contributed to no doubt by the relative ease of differential chemical analysis. Though the sequence of events leading from digestion of the various sugars to post-absorptive transportation and utilization is fairly well understood, the details of the selective absorption mechanism are still challenging.

Site of absorption. In natural foodstuffs carbohydrate is found mostly in the form of polysaccharides, especially starch and glycogen. These are in colloidal form but are broken down to glucose by the enzymatic action of diastases. The disaccharides—maltose, sucrose and lactose—are found in lesser quantities, and the hexoses—glucose, galactose and fructose—and the pentoses in respectively small quantities still.

There is practically no absorption of carbohydrate in the stomach, though glucose absorption can take place from this site in the presence of concentrations in the neighborhood of 40 per cent or greater (14, 36). Absorption of sugars by the colon has also been questioned. It has been reported that monosaccharides are not absorbed from the large intestine of the rat or dog (37, 38). The guinea pig, however, can absorb glucose rapidly from a distended cecum, a process not inhibited by phlorhizin, and from other sites in the colon as well when the concentration is 40 per cent or greater (39). At this concentration the translocation of the sugar may be a manifestation of diffusion resulting from damage to the mucosa. Little if any absorption takes place from the human rectum (40).

The main site of sugar absorption is the small intestine. Many investigators have shown that the absorption of glucose is greater in the proximal than in the distal small bowel, though there are conflicting reports as to whether absorption is maximal in the duodenum (42, 43, 44). *In vitro* studies of progressive segments of small intestine reveal that glucose translocation decreases proportional to the distance toward the ileocecal valve, but for technical reasons the duodenum can not be included in this statement (22, 45).

Post-absorptive transportation. Though it has been accepted that the sugar or its metabolites pass directly to the blood stream after translocation, there is evidence that varying amounts appear in the lymph. Information necessary to the solution of this question has been derived, however, from glucose tolerance curves and comparative analyses of reducing substances in both channels, neither method of which is completely satisfactory. Some support for the portal route is derived from the studies of Sherlock and Walshe (46) and others (47, 48) who noted that superficial anastomotic veins in patients with portal cirrhosis show significant rises in glucose and fructose levels during their respective absorptions, and these levels are higher than that in blood from the antecubital vein.

The influence of concentration on absorption. Hewitt (49), in 1924, studying glucose absorption in rats, reported that the rate of absorption varied directly with concentration. Cori (6), in his classic report a year later, could not confirm this and in fact demonstrated there was no difference in absorptive rates with varying concentration. "Cori's law" was then established that the rate of glucose absorption is independent of concentration. In retrospect, Hewitt was working with glucose concentrations of less than 5 per cent while Cori used concentrations of 25, 50 and 80 per cent. By studying concentrations over both ranges, Groen (12) showed that there was a direct relationship of concentration to absorptive rate up to a 10 per cent concentration, above which the rate was constant, thus clarifying the relationship. There is, apparently, a fixed concentration of glucose (approximately 10 per cent) above which the rate of absorption is constant. Cori (6) showed that, even after absorption of a 70 per cent of a glucose solution from the gut lumen, the rate had not diminished.

In man, Shay et al. (14) demonstrated that the stomach and, to a greater degree the duodenum, are capable of diluting concentrated glucose solutions, and in so doing rendering them isotonic. These same authors (15) later demonstrated that gastric emptying is inhibited proportionally to the glucose concentration. Abbott et al. (50) showed that, regardless of the concentration of glucose ingested, the concentration in the jejunum and ileum is generally less than 5 per cent (isotonic 5.4 per cent). Even if the duodenal and upper jejunal sugar contents are hypertonic, while the lower jejunal and ilial contents are isotonic, the total osmotic pressure of the lumenal mixture remains close to 300 mOsm. per L. (isotonic). A concentrated glucose solution in the upper intestine mobilizes a hypotonic fluid gaining volume, while a hypotonic solution loses volume and, concomitantly, there is a decrease in chloride proportional to the rise in concentration of glucose.

The influence of other factors on absorption. A variety of other factors have been reported to influence the rate of sugar absorption. Several components of the vitamin B complex are necessary for the formation of enzymes and co-enzymes of prosthetic groups which are essential to the mechanism of absorption. Althausen (51) showed that a dietary deficiency of vitamin B complex would lead to a decrease in glucose absorption, though xylose transfer was unchanged. Cori and Cori (52) found that rats starved for 48 hours absorbed less fructose than rats starved for 24 hours, while McDougall (28) showed that this was true for glucose also. Westenbrink found that, if an animal was fed with glucose, fructose or galactose for two days or more, its capacity for absorbing the respective sugar was increased (28). It is possible that this adaptation to diet is due to stimulation of specific enzymes in the intestinal mucosa, while the opposite is true with sugar deprivation.

Several endocrine glands appear to influence glucose absorption. Wilbrandt and Lengyel (53) demonstrated that glucose absorption was markedly decreased by adrenalectomy in the rat, while xylose absorption was not affected. This inhibitory action could be prevented with adrenal cortical hormone. Posterior pituitary extract has also been shown to reduce glucose absorption by 50 per cent (54). Removal of the hypophysis, ovaries or thyroid is followed by a decrease in intestinal absorption of glucose (51). Althausen and Stockholm (55) showed that giving thyroid hormone to normal rats to increase the BMR by 50 per cent could produce a marked increase in absorption of glucose, galactose and xylose.

The influence of physical variations in blood flow through the intestinal wall on absorption is not clear. It can be shown that the quantity of blood flowing through the intestinal wall is much increased during digestion and absorption (28). Evidence has suggested that sugar absorption is related to motility. Cummins and Almy (10) demonstrated this by intubating the upper small intestine and inducing hypermotility with drugs. The mechanism is unknown but may be connected with an increase in the intestinal blood flow. Jones (56) stated that there is an apparent limit to increments in rates of absorption and possibly total absorption as far as motility is concerned. Obviously with markedly increased rates of motility there will be a point at which absorptive processes are decreased, because of decreased exposure of absorbable material to the mucous membrane.

The contribution of villous activity to sugar absorption is also debatable. Though the rhythmic pumping of villi has been observed, the region of greatest activity does not necessarily correspond to the region of greatest glucose absorption (44), and in general there is no correlation between the degree of activity and the rate of glucose absorption (57). Still, Magee and Reid (58) noted that the pumping of villi in the cat's intestine was greatest at 13.5 per cent glucose concentration, the known optimal concentration for glucose absorption in other animals.

There is little information available on the influence of intraluminal pressure on absorption. Nasset and Parrey (59) demonstrated that glucose absorption is independent of intraintestinal pressure between limits of 5 and 25 cm. of the glucose solution below atmospheric. *In vitro* the rate of glucose absorption is proportionately increased up to 10 cm. hydrostatic pressure (22), while with greater pressures there is no change (45).

As early as 1902 Nagano (42) challenged the previously held belief that translocation of a sugar was proportional to its molecular weight by showing that certain six-carbon sugars were absorbed more quickly than five-carbon sugars. He further found variations in the absorptive rates of individual sugars, with galactose, glucose, fructose, mannose, xylose and arabinose being absorbed in that order. Though Nagano's results were disputed for many years, in 1925 they were confirmed by Cori (6). Verzar and Laszt (1935) further distinguished between glucose and galactose—which seemed to be absorbed at a constant rate regardless of concentration—and xylose, sorbose and mannose—whose rate of absorption was related to concentration (28). These authors first suggested that there was an active process involved in the absorption of certain sugars. It had been discovered earlier that there is mutual inhibition of absorption of glucose and galactose; the total amount of both absorbed is no more than if only one is given (60). This suggested that both are absorbed by the same process and that there is a limiting factor other than the total amount of sugar present and their concentrations.

That glucose, galactose and fructose are absorbed by a selective and specific mechanism was clearly demonstrated in later years. Fisher and Parsons (45), Wilson and Wiseman (18, 61), Darlington and Quastel (16), Korelitz and Frank (22), and Wilson and Vincent (62) all showed that aerobically glucose is transferred against a concentration gradient while anaerobically (or when oxygen is replaced by nitrogen) the glucose transfer is equivalent to that expected by diffusion alone. Galactose and fructose are also transported aerobically against a concentration gradient. Fructose absorption differs from the other two, however, in that glucose appears in the outer solution in much greater quantities that fructose. The small amount of fructose that is transferred as fructose can be accounted for by diffusion alone. Mannose, sorbose, xylose, arabinose and ribose are not transported against a concentration gradient; their transfer is directly proportional to concentration. There is apparently no selective mechanism for their transport.

That an active respiratory system is essential for the selective absorption was shown not only by the inhibiting influence of anaerobiosis, but also by the inhibitory effects of phlorhizin, monoiodoacetic acid, 2,4-dinitrophenol, cyanide, azide, fluoroacetate, malonate and chloretone (16, 45, 63, 64). Diffusion of sorbose or, fructose is not altered by these. The nature of this selective mechanism remains to be elucidated.

Phosphorylation theory. When it was shown that the addition of a phosphate buffer at pH 7 increased the rate of glucose absorption in rats, the theory was initiated that glucose might be transformed into a phosphate compound in the mucosa during absorption (58). Though it was later shown that the accelerating action of the phosphate was a pH effect (65), further investigation was stimulated.

It is known that both mono-iodoacetic acid and phlorhizin inhibit phosphorylation and they also hinder glucose and galactose translocation in the intestine (28, 45, 63, 64, 66, 67). It has also been demonstrated that organic phosphate increases in the mucosa during glucose absorption (68, 69). With this indirect evidence and the knowledge that phosphorylation played an important part in the intermediary metabolism of glucose elsewhere, a similar mechanism was felt to be active in glucose and galactose absorption. The phosphorylation theory then explained selective absorption as dependent upon the conversion of the hexose within the epithelial cell of the intestinal mucosa to a hexose phosphate. Since there would be no unconjugated free glucose or galactose within the cell a steep gradient is obtained which favors the continuous translocation across the epithelial membrane.

The phosphorylation theory has been challenged on many occasions during the past few years. No significant change in concentrations of several acid-soluble phosphate fractions was found in the mucosa when the glucose absorptive rate was altered by influencing thyroid activity (70). There was no difference in the phosphate content of various areas of mucosa which are known to absorb glucose at different rates. It was also shown *in vitro* that the presence of phosphate is not necessary for active glucose absorption (16). Evidence was presented that monoiodoacetic acid and phlorhizin were general tissue poisons and do not act specifically by inhibiting phosphorylation but more likely interfere with the utilization or coupling of energy bonds (64).

A great deal of support for the phosphorylation theory stemmed from experiments in which the inhibited selective absorption of glucose and galactose was compared to the uninhibited diffusion of xylose. Davidson and Garry (71) showed, however, that xylose is absorbed as rapidly as glucose from the distal small intestine of cats, emphasizing the problem of species differences. To further challenge the theory that all pentoses were absorbed by diffusion, it was shown that xylose and mannose are also phosphorylated (72, 73). Studying homogenates of rat intestine, Sols (73) compared the rates of absorption of many sugars with their rates of phosphorylation and found a serious lack of correlation between the two.

Although the evidence suggests that phosphorylation is involved in the transfer mechanisms for sugars, there is no proof of its exact role in active absorption.

In vitro studies of active mechanisms. The results of *in vitro* studies have raised an alternative explanation for selective sugar absorption. Hestrin-Lerner and Shapiro (21) reported that 30 to 60 per cent of glucose disappearing from the perfusing mucosal solution could be identified as a non-reducing substance in the serosal solution. Further investigation *in vivo* revealed that during absorption the concentration of radio-active material was higher in the portal vein than in the aorta, though the concentration of radio-active reducing substances was less (24). A considerable amount of radio-activity associated with a non-fermentable substance was found in the intestinal wall as well. They proposed that a non-fermenting glucose metabolite is formed in the intestine during glucose absorption and passes to the portal blood as such, the process maintaining a high concentration gradient for glucose between the lumen and the cell.

This theory is disputed in that other investigators have found considerable amounts of lactic acid in the serosal solutions which could represent the unidentifiable non-fermenting metabolite described above (18, 74). Still others (17, 22, 45) have identified glucose as such in the serosal solutions, suggesting that the whole question of the metabolite theory is artifactual and attributable to inadequate oxygenation of the intestinal mucosa.

Absorption of fructose and sucrose. In vitro studies have revealed that fructose is converted to glucose in the process of absorption, any transfer of fructose as such being attributable to diffusion (16, 75). Since diffusion is proportional to concentration, it is understandable that with large concentrations of perfusing fructose solutions, more fructose will be transferred without conversion to glucose.

Sucrose is partially broken down within the intestinal wall and appears on the serosal side as glucose and fructose as well as sucrose (75). As with fructose perfusion, the amount of sucrose translocated as such is proportional to concentration. With increasing concentration the percentage of perfusing sucrose translocated as glucose will fall, while that translocated as sucrose rises and fructose remains constant.

In summary, it is well substantiated that sugars are absorbed predominantly from the small intestine, more in the proximal than the distal, and that above a concentration range of 10 to 13 per cent the rate of absorption is independent of concentration. The presence of a selective mechanism for the absorption of glucose, galactose and fructose has been verified, while in contrast other monosaccharides are translocated according to simple physical laws. The exact nature of the selective mechanism has in no way been clarified. Though phosphorylation is involved in the process in some manner, evidence has not supported this as the entire explanation. A better understanding of the interrelationships and influences of the hexokinase and other enzyme systems will probably be necessary for the final solution.

PROTEIN ABSORPTION

Until recently information on the mechanism of protein absorption was scanty In the 19th century it was assumed that protein was absorbed as peptones and proteases. Later all the known amino acids were discovered in the intestine during absorption (76) and the identification of enzymes which split peptones and the proteases rounded out the picture (28).

Though it is recognized that proteins are absorbed as amino acids there have been suggestions that protein is also absorbed in larger forms. Though the impermeability of the intestinal mucosa for colloidal particles makes the absorption of polypeptides unlikely, the appearance of various naturally occurring proteins in the portal blood and especially the lymph has been found in the investigation of allergic phenomena (77, 78). It has been further argued that some protein complexes must get through as indicated by the functional integrity of ingested thyroid extract. Theoretically dipeptides should then be transferred more easily There is some evidence that these are absorbed in small quantities but never to a marked degree (19, 79).

Site of absorption. There is little evidence that protein is absorbed at any other site than the small intestine, though absorption by the stomach has been reported by many earlier workers (28). It has been suggested that under physiological conditions the products of digestion leave the stomach too quickly for absorption to take place there. Amino acids are almost entirely absorbed in the small intestine; if any enter the large intestine they are probably absorbed to a small extent but are partially destroyed by bacteria. Amino acids probably diffuse through rectal mucosa as well (80). *In vitro* study has revealed that alanine is absorbed to a greater extent in the jejunum than in the ileum (22). After translocations of the amino acids they are transported in the portal system and to a lesser degree in the lymph (28, 81). When larger forms of protein are absorbed they are found predominantly in the lymph (78).

Influence of concentration on absorption. The effect of amino acid concentration on absorption is not as well established as in the case of glucose. *In vitro* the rate of appearance of alanine in serosal solution is proportional to its concentration in the intestinal lumen. (82). The greatest rate of increase occurs over a range of low concentrations above which the absorptive rate is constant. In this regard amino acid absorption would be similar to the selective absorption of sugar. It has been suggested that a saturation of the intestine with the amino acid is necessary before any is translocated (19) or that saturation is the limiting factor in absorptive rate (82). It would seem reasonable that saturation is the limiting factor in rate of absorption, but transfer of amino acid would occur at increasing rates proportional to increasing concentration until saturation is reached.

Selective mechanisms. Just as with glucose the absorption of amino acids had until recently been considered by most workers in the field a matter of simple diffusion (81, 83). After Hober and Hober (1937) (84) emphasized that there was an active mechanism for amino acid absorption, many authors were able to demonstrate by various techniques that in racemic mixtures of an amino acid the *L*-isomer is transferred more rapidly than the *D*-isomer, with which the rate is consistent with diffusion alone (85, 86, 87, 88). With the introduction of *in vitro* method many workers were able to show that the *L*-isomer of methionine, alanine, phenylalanine, histidine, isoleucine, glycine and proline could be translocated against a concentration gradient, while the *D*-isomers could not (17, 19, 61, 89, 90). This active transfer could be blocked by anaerobiosis, cyanide and dinitrophenol but not by phlorhizin (19, 22, 82). Kuroda and Gimbel (91) showed that the disappearance of the *L*-isomers was greater than that of the *D*-isomers from an *in vivo* loop of human intestine.

Other amino acids including glutamic acid, aspartic acid, lysine and ornithine are not actively transferred (17, 19, 90). The glutamic or aspartic acid lost from the intra-luminal space could not be recovered from either the outer solution or the intestinal wall (17). When glutamic acid alone was perfused through both the inner and outer solutions, the presence of alanine was discovered in both solutions, the outer more than the inner, at the end of the test period. When aspartic acid alone was perfused, both alanine and glutamic acid could be found in the outer solution. When other amino acids were perfused individually the transfer of only that specific amino acid as such could be demonstrated.

As with the hexoses competing for the common selective mechanism of absorption, mutual inhibition has been demonstrated for amino acids (90, 92). Some actively transported *L*-amino acids when perfused alone were transferred at comparatively low rates (methionine and histidine). When perfused in combinations these would hinder the transfer of other amino acids (prolene and glycine) which would individually be transferred at a comparatively high rate. The *L*-amino acids not moving against a concentration gradient (glutamic, lysine and ornithine) had no effect on the transfer of amino acids for which there is an active mechanism. Those that are transferred at a rapid rate did not hinder those that are more slowly transferred. Kamin and Handler (93) performed experiments which showed that this competition was of little consequence in comparison to that exerted in the renal reabsorption of amino acids.

Phosphorylating processes have been implicated as in selective carbohydrate absorption. Since phlorhizin inhibition is one of the mainstays of the phosphorylation theory of carbohydrate absorption, the failure of phlorhizin to inhibit selective amino acid absorption is a telling argument.

To summarize, amino acids are absorbed predominantly by the small intestine and it appears that as with glucose there is a limiting concentration above which the absorptive rate is constant. The presence of a selective mechanism for amino acid absorption is verified by experiments showing that there is translocation against a concentration gradient and the preferential absorption of the *L*-versus the *D*-isomer. Even among the *L*-isomers it appears that the mono-amino-mono-carboxylic acids are transferred while the di-amino acids (lysine, ornithine) are not, demonstrating selectivity in the active mechanism. Evidence suggests that while glutamic acid and aspartic acid are not actively transferred, they are involved in a trans-amination process, although they are probably partially metabolized as well.

The intricate nature of the active and selective mechanism is not understood but again is probably intimately associated with specific enzyme systems and utilization of energy.

WATER ABSORPTION

Site. Water is probably absorbed from all sites in the gastro-intestinal tract. Though early studies could not demonstrate absorption from the stomach, it is now suggested that up to 2.5 per cent of administered D_2O may be absorbed per minute from this site (95, 96, 97). Considerable water absorption from the colon has been established (28). The main site of water absorption is the small intestine where Lee et al. (97) showed a water loss of 23 per cent per minute.

Hormonal and mercurial influence on water absorption. In general water translocation *per se* is not influenced by hormones except passively as its solutes are affected. Pitressin, however, produces a significant increase in the absorption of water from isosmotic saline, though this is not necessarily of physiologic significance (98). Addition of mercuhydrin to test solutions in the gut is accompanied by decreased rates of absorption of sodium, chloride and water, an effect which is decreased with repeated use of the drug (99). This suggests a similarity between intestinal mucosa and renal epithelium in this respect. A similar result follows the administration of $HgCl_2$.

Mechanism of water absorption. Water transfer between blood and intestinal lumen is influenced by so many other factors that the presence of a selective mechanism for this purpose is questionable. To confirm the presence of a selective mechanism it would be necessary to demonstrate an accelerated transfer of water beyond that expected by diffusion and independent of ion transportation.

Early experiments demonstrated the basic prerequisites that permeability for water occurs in both directions across the intestinal wall (28), that crystalloids diffuse from gut to blood, according to their diffusion velocities (100, 101, 102, 103) and that crystalloids can at least enter the intestine from the blood (104, 105). It was shown in both animal and human experiments that the osmotic pressure of intestinal contents becomes equal to that of the blood by virtue of water and electrolyte shifts which were considered to take place according to the physical laws of diffusion and osmosis (12, 50, 101). Further support for this was given by Verzar and McDougall (28) who showed that a solution of selectively absorbed glucose becomes isotonic before water leaves the intestine, while from a passively absorbed xylose solution the xylose will diffuse into the blood and be replaced by blood crystalloids with resulting maintenance of isotonicity but no water absorption.

Not all investigators have accepted the transfer of water according to simple physical laws. Visscher and his co-workers (106, 107) showed that univalent ions can be concentrated in the intestine to levels above the blood concentration, a process which could be hindered by the presence of other anions or cations of valence greater than one. The lowering of the univalent ion concentration in the lumen would have to be accompanied by diffusion of this ion against a concentration gradient, requiring osmotic work. It was also shown in D_2O experiments that while the concentration of chloride ion moving out of the lumen is proportional to the concentration in the lumen, the apparent concentration of chloride moving into the lumen is practically independent of its concentration in the blood (108). Such being the case, the lumenal solution should become hypotonic and influence water absorption in this way. This school later showed in calculating the ratio of total directional rates (blood to gut and gut to blood) to net transport rates of water that there was a 200 fold difference between that derived experimentally and that expected on the basis of diffusion (109).

Another school has suggested that water is transported neither by simple physical laws nor by an active mechanism but rather as an obligatory carrier of a selectively absorbed substance. Wilson and Wiseman (18) showed that the translocation of water in the presence of glucose or methionine is inhibited by anaerobiosis. In the *in vitro* apparatus with glucose solution on the mucosal side and bicarbonate solution without glucose on the serosal side, translocation of water (along with glucose) continues contrary to what would be expected by osmosis (110).

A few words should be devoted to the influence of colloidal osmotic pressure and hydrostatic pressure on water transfer. Each of these factors has been proposed to explain the translocation of both the water and its solutes after isotonicity has been established within the lumen. Such explanations would be necessary if water were considered transported by simple physical laws. According to "Starling's Law," though the concentration of diffusible solutions on either side of the intestine must be equal, the plasma colloids have a higher osmotic pressure than the colloids of the intestinal solution and water must then pass into the blood. The resulting increase in salt concentration in the lumen would be followed by a diffusion of salts into the blood.

It has been reported that water absorption increases as a linear function of pressure (111), though *in vitro* studies disprove this for pressures greater than 10 cm. in animal intestine (1). It is known, however, that the colonic pressure may rise to as high as 40 cm. of water (28), possibly explaining the almost complete absorption of isotonic solutions from this site. The presence of large amounts of fluid in the small intestine, by increasing the hydrostatic pressure, might exert an influence there as well.

In summary, though the means of water absorption is not at all clear at present, it appears that there is no active mechanism for this purpose. There is, however, an active mechanism for the absorption of electrolytes. The electrolytes pass from the lumen to the blood according to diffusion velocities and osmotic laws, while the passage from blood to lumen is much more complex, probably influenced by multiple factors. It is the latter mechanism that is responsible for active electrolyte absorption, while water absorption is influenced secondarily. The organic solutes for which there is a selective absorptive mechanism will, during their transfer, also carry an obligatory amount of water. Colloidal osmotic and hydrostatic factors probably physically influence water transfer but are minor factors in net transport.

IRON ABSORPTION

Though this subject has been adequately and frequently reviewed (112), discussion of the specific mechanism involved in iron absorption is pertinent for an understanding of absorption in general. It is well recognized that iron must be present in the ferrous form in order to be absorbed. In natural foodstuffs iron is mostly contained as ferric hydroxide or ferric-organic chelates (citrate, lactate, amino acids). Both hydrochloric and organic acids serve to break down the iron compounds to ferric ions or loose ferric chelates which can be readily reduced to ferrous ions by such reducing agents as ascorbic acid and sulfhydryl compounds present in food.

Since iron once absorbed is almost completely retained by the body, some mechanism for iron regulation must exist to prevent excess absorption but still permit adequate amounts to be absorbed. This mechanism is known to exist along the entire small intestine, though the region of most active absorption is the first part of the duodenum. Chronically anemic dogs were found to absorb iron at a rate of 5 to 15 times greater than normal (113). This response would not follow a sudden bleeding but would occur only after several days, suggesting a correlation between iron absorption and iron reserves in the body. After administration of iron, the degree of resistence to further absorption could be shown to increase rapidly for several hours, and remain constant for several days, then gradually decline. Hahn et al. (113) suggested that there was a mucosal block which was probably explained by a temporary storage of iron.

Granick (114) then described the presence of ferritin crystals, consisting of clusters of ferric hydroxide attached in four discrete areas to a protein, in the small intestinal mucosa, especially the duodenum. Several hours after a single iron feeding the increased concentration and the distribution of the ferritin crystals remained constant, and after the maximum iron feeding it would take six days before the mucosal ferritin content would approximate normal. He reasoned that the involved protein (apoferritin) was constantly produced and broken down in the mucosal cells but, if protected by adhering ferric hydroxide clusters forming ferritin, it would accumulate. It would follow that ferritin should increase in response to iron feeding. The time sequence of the change in ferritin content in general paralleled that of the appearance and disappearance of the mucosal block.

Ferritin has been demonstrated in both fixed tissue histiocytes and the columnar epithelial cells. In the tips of duodenal villi, Granick (114) found histiocytes containing yellow or green vacuoles. After a few days of iron feeding, the vacuoles and associated granules in the histiocytes would stain dark grey to black. The granules were sometimes observed in the columnar cells. Granick suggested that the columnar cells may be the site of origin of the ferritin while the histiocytes function primarily as a protective mechanism by taking up excess amounts of iron into their vacuoles.

The means by which iron absorption proceeds from the stage of intra-mucosal ferritin is not clear. A protein (transferrin, siderophilin) has been identified which serves to transport iron in an Fe-transferrin complex. It is likely that transferrin picks up the iron as it leaves the mucosal cell, though this one step has not been demonstrated. It has been shown that the rate of movement of iron from the mucosal cells into the blood stream is independent of the degree of transferrin saturation with iron. A lowered oxygen tension, however, has been correlated with an increased rate of removal of iron from the cells. Granick (114) suggested that the iron leaves the ferritin complex and the mucosal cell in ferrous form where it is immediately auto-oxidized to the ferric state and transported away attached to a specific component of the globulin fraction (transferrin or otherwise). This explanation would require a preliminary step of reduction of the ferric iron of the ferritin.

It appears that both the mucosal block and the completion of iron translocation involve a complicated series of iron oxidation and reduction reactions. The physiologic mechanism of ferrous iron saturation, the influence of storage and serum iron on the absorptive rates, the uni-directional movement of the iron in the epithelial cells and the form and means of transfer from the cell to the portal system are yet to be explained. It has been proven that the iron is transported by the portal blood and not by the lymph (115, 116, 117).

There is no strong evidence that organ systems other than the pancreas influence the absorption of iron. It has been shown that ligation of pancreatic ducts will promote an increased deposition of iron in the liver (118, 119, 120), though this has not been shown to be true in all animal species. The mechanism is not understood.

SUMMARY

It seems clear that the products of digestion of the major food stuffs of the diet, and the accessory food factors (electrolytes, vitamins) are absorbed across the intestinal cell by selective processes of active transport, which require the expenditure of energy and spatially orientated enzyme systems. The details of these intracellular processes of translocation are almost completely unknown at present.

Absorption of neutral fat requires the hepatic secretion of bile salts and the pancreatic secretion of lipase, and occurs throughout the entire small intestine, perhaps to a greater extent in the distal half. Neutral fat need not be hydrolyzed completely before absorption, but the major portion of dietary fat is split to monoglycerides, fatty acids and glycerol in the intestinal lumen. Long-chain fatty acids appear in the mesenteric lymph as triglycerides, short-chain fatty acids enter the portal vein as such along with glycerol. Active transport of lipid across the intestinal cell is involved in this process, but the details are obscure. The role of phosphorylation in this translocation is not fully established.

Carbohydrates are absorbed predominately as monosaccharides and more by the proximal than the distal small intestine. Above a concentration range of 10 to 13 per cent, the absorption rate is independent of concentration. This is of little importance under physiological circumstances, however, since inhibition of gastric emptying and dilution of concentrated solutions in the duodenum serve to render solutions isotonic. A selective mechanism for the absorption of glucose, galactose and fructose has been verified while other monosaccharides are translocated passively. A phosphorylation theory has been offered to explain the selective absorption, and though phosphorylation is involved, it does not appear to be a complete explanation. *In vitro* studies have opened new fields of investigation in carbohydrate absorption, and some new light has been shed on fructose and sucrose transfer.

Protein is absorbed predominately as amino acids, and again there is a limiting concentration above which the absorptive rate is constant. The presence of active and selective mechanisms for amino acid absorption is confirmed by the demonstration of intestinal transfer against concentration gradients and by preferential absorption of the *L*-isomer. Among the *L*-isomers the mono-amino-monocarboxylic acids are transferred while the di-amino acids are not.

It appears that there is no demonstrable active mechanism for water absorption but there is one for electrolytes. While the latter pass from intestinal lumen to blood according to diffusion velocities and osmotic dictates, movement in the opposite direction is more complex. Water transfer is dependent on electrolyte transfer and the selective absorption of organic solutes. Colloidal, osmotic and hydrostatic factors are of less importance in net water transport.

The mechanism for iron absorption is unique in that the amount absorbed is controlled by the body's need. The present knowledge of the apoferritin-ferritin process in the mucosal mechanism and subsequent completion of iron absorption are reviewed.

REFERENCES

1. Fisher, R. B., and Parsons, D. S.: A Preparation of Surviving Rat Small Intestine for the Study of Absorption. J. Physiol., 110: 36, 1949.
2. Davson, H., and Danielli, J. F.: The Permeability of Natural Membranes. Cambridge, 2nd Edition, 1952.
3. Baker, J. H.: The Free Border of the Intestinal Epithelial Cell of Vertebrates. Quart. J. Micro. Sciences., N.S., 84: 73, 1942.
4. Granger, B., and Baker, R. F.: Electron Microscope Investigation of the Striated Border of Intestinal Epithelium. Anatomical Record, 107: 423, 1950.
5. Sjöstrand, F., and Zetterquist, H.: Structure of Intestinal Mucosa. Progress In the Chemistry of Fats and Other Lipids. Pergamon Press, London. N. Y., Vol. 3: P. 388, 1955.
6. Cori, C.: The Fate of Sugar in the Animal Body. J. Biol. Chem., 66: 691, 1925.
7. Miller, T. G., and Abbott, W. O.: Intestinal Intubation: A Practical Technique. Am. J. Med. Sc., 187: 595, 1934.

8. Abbott, W. O., and Miller, T. G.: Intubation Studies of the Human Small Intestine. III. A Technique for the Collection of Pure Intestinal Secretion and For Study of Intestinal Absorption. J.A.M.A., 106: 16, 1936.
9. Cummins, A. J.: Absorption of Glucose and Methionine from the Human Intestine; The Influence of the Glucose Concentration In the Blood and In the Human Lumen. J. Clin. Invest. 31: 928, 1952.
10. Cummins, A. J., and Almy, T. P.: Studies on the Relationship Between Motility and Absorption in the Human Small Intestine. Gastroenterology, 23: 179, 1953.
11. Cummins, A. J., and Jussilar, R.: Comparison of Glucose Absorption Rates In the Upper and Lower Human Small Intestine. Gastroenterology, 29: 982, 1955.
12. Groen, J.: The Absorption of Hexoses From the Upper Part of the Small Intestine in Man. J. Clin. Invest. 16: 245, 1937.
13. Nicholson, J. T. L., and Chornock, F. W.: Intubation Studies of the Human Small Intestine. An Improved Technique for the Study of Absorption; Its Application to Ascorbic Acid. J. Clin. Invest. 21: 505, 1942.
14. Shay, H., Gershon-Cohen, J., Fels, S. S., and Munro, F. L.: The Absorption and Dilution of Glucose Solutions in the Human Stomach and Duodenum. Am. J. Dig. Dis., 6: 535, 1939.
15. Shay, H., Gershon-Cohen, J., Fels, S. S., and Munro, F. L.: The Fate of Ingested Glucose Solutions of Various Concentrations At Different Levels of the Small Intestine. Am. J. Dig. Dis., 7: 456, 1940.
16. Darlington, W. A., and Quastel, J. H.: Absorption of Sugars from Isolated Surviving Intestine. Arch. Biochem., 43: 194, 1953.
17. Wiseman, G.: Absorption of Amino-Acids Using an In-Vitro Technique. J. Physiol. 120: 63, 1953.
18. Wilson, T. H., and Wiseman, G.: The Use of Everted Small Intestine for the Study of the Transference of Substances from the Mucosal to the Serosal Surface. J. Physiol., 123: 116, 1954.
19. Agar, W. T., Hird, F. J. R., and Sidhu, G. S.: The Active Absorption of Amino-Acids By the Intestine. J. Physiol., 121: 255, 1953.
20. Smyth, D. H., and Taylor, C. B.: Transport of Water and Other Substances Through the Intestinal Wall. J. Physiol., 126: 42P, 1954.
21. Hestrin-Lerner, S., and Shapiro, B.: Active Absorption of Glucose From the Intestine. Nature, 171: 745, 1953.
22. Korelitz, B. I., and Frank, E. D.: In-Vitro Contributions to the Knowledge of Carbohydrate and Protein Absorption. In Preparation.
23. Wilson, T. H.: A Modified Method for Study of Intestinal Absorption In-vitro. J. Appl. Physiol., 9: 137, 1956.
24. Hestrin-Lerner, S., and Shapiro, B.: Absorption of Glucose from The Intestine. Biochim. Biophs., Acta, Amst. 13: 54, 1954.
25. Bollman, J. L., Cain, J. C., and Grindley, J. H.: Techniques for the Collection of Lymph from the Liver, Small Intestine, or Thoracic Duct of the Rat. J. Lab. and Clin. Med., 33: 1349, 1948.
26. Kremen, A. J., Linner, J. H., and Nelson, C. H.: An Experimental Evaluation of the Nutritional Importance of Proximal and Distal Small Intestine. Ann. Surg. 140: 439, 1954.
27. Benson, J. A., and Chandler, G. N., VanSteinhayse, F. E., and Gagnon, J. O.: Studies Concerning the Rate of Fat Absorption in the Small Intestine of the Rat. Gastroenterology, 30: 37, 1956.
27a. Haselwood, G. A. D.: Recent Developments in our Knowledge of Bile Salts. Physiol. Rev., 35, 178, 1955.
28. Verzar, F., and McDougall, E. J.: Absorption from the Intestines. Longmans, Green and Co., London. 1936.
29. Frazer, H. C.: Mechanism of Intestinal Absorption of Fat. Nature, 175: 491, 1955.
30. Bloom, B., Chaikoff, I. L., Reinhardt, W. O., Entenman, C., and Dauben, W. G.:

The Quantitative Significance of the Lymphatic Pathway in Transport of Absorbed Fatty Acids. J. Biol. Chem., 184: 1, 1950.
31. Reiser, R., Bryson, M. J., Varr, M. J., and Kurken, K. A.: The Intestinal Absorption of Triglycerides. J. Biol. Chem., 194: 131, 1952.
32. Bloom, B., Chaikoff, I. L., and Reinhardt, W. O.: Intestinal Lymph as Pathway for Transport of Absorbed Fatty Acids of Different Chain Lengths. Am. J. Physiol., 166: 451, 1951.
33. Börgstrom, B.: On The Mechanism of The Intestinal Fat Absorption. III. Acta. Physiol. Scand., 25: 140, 1952.
34. Sinclair, R. G.: The Role of The Phospholipids of The Intestinal Mucosa in Fat Absorption. J. Biol. Chem., 82: 117, 1929.
35. Bergström, S., and Borgström, B.: The Intestinal Absorption of Fats. Progress in the Chemistry of Fats and Other Lipids. Pergamon Press, London, N. Y., Vol. 3: 351, 1955.
36. Morrison, J. L., Shay, H., Ravdin, I. S., and Cahoon, R.: Absorption of Glucose from the Stomach of the Dog. Proc. Soc. Exp. Biol. Med., 41: 131, 1939.
37. Davidson, J. M., and Garry, R. C.: Absorption of Monosaccharides from Large Intestine of Rat Under Urethane Anaesthesia. J. Physiol., 96: 172, 1939.
38. McNealy, R. W., and Willems, J. D.: Absorption of Glucose from Colon; Preliminary Study of Glucose Enema. Surg. Gynec. Obst., 49: 794, 1929.
39. Hagen, P.: The Absorption of Monosaccharides from the Gastro-Intestinal Tract of the Guinea-Pig. Austral. J. Exp. Biol. Med. Sci., 30: 527, 1952.
40. Garrer, A. H., Groen, J., and Hallen, L.: The Absorption of Glucose from the Human Rectum. Acta. Med. Scand., 107: 1, 1941.
41. Ebeling, W. W.: Absorption of Dextrose from the Colon. Arch. Surg., 26: 134, 1933.
42. Nagano, J.: Pflüger's Arch., 90: 389, 1902. Cited by Verzar, F., and McDougall, E. J. (28).
43. London, E. S., and Polowzowa, W. W.: Z. Physiol. Chem., 57: 529, 1908. Cited by Verzar, F., and McDougall, E. J. (28).
44. King, C. E., Arnold, L., and Church, J. G.: The Physiological Role of the Intestinal Mucosal Movements. Am. J. Physiol., 61: 80, 1922.
45. Fisher, R. B., and Parsons, D. S.: Glucose Absorption from Surviving Rat Small Intestines. J. Physiol., 110: 281, 1950.
46. Sherlock, S., and Walshe, V.: The Use of A Portal Anastomotic Vein for Absorption Studies in Man. Clin. Sci., 6: 113, 1946.
47. Billings, F. T., Jr., and DePree, H. E.: Diagnosis of Portal Vein Obstruction; Studies of Intestinal Absorption of Glucose Using Abdominal Collaterol Veins. Bull. Johns Hopkins Hosp., 85: 183, 1949.
48. Bean, W. B., Franklin, M., Embick, J. F., and Daum, K.: Absorption Studies Using Portal Anastomotic Veins. J. Clin. Invest., 30: 263, 1951.
49. Hewitt, J. A.: The Metabolism of Carbohydrates Pt. III. The Absorption of Glucose, Fructose and Galactose from the Small Intestine. Biol. Chem. J., 18: 162, 1924.
50. Abbott, W. O., Karr, W. G., and Miller, T. G.: Intubation Studies of the Human Small Intestine: VII. Factors Concerned In Absorption of Glucose from the Jejunum and Ileum. Am. J. Dig. Dis., 4: 742, 1938.
51. Althausen, T. L.: Hormone and Vitamin Factors In Intestinal Absorption. Gastroenterology 12: 467, 1949.
52. Cori, C. F., and Cori, G. T.: Fate of Sugar In Animal Body; Sugar Oxidation and Glycogen Formation In Normal and Insulinized Rats During Absorption of Fructose. J. Biol. Chem., 73: 555, 1927.
53. Wilbrandt, W., and Lengyel, L.: Z. Bio. Chem., 267: 204, 1933. Cited by Verzar, F., and McDougall, E. J. (28).
54. Cori, C. F.: Mammalian Carbohydrate Metabolism. Physiol. Rev., 11: 143, 1931.

55. Althausen, T. L., and Stockholm, M.: Influence of Thyroid Gland on Absorption in Digestive Tract. Am. J. Physiol., 123: 577, 1938.
56. Jones, C.: Discussion on Cummins, A. J., and Almy, T. P. Gastroenterology, 23: 179, 1953.
57. Wells, H. S., and Johnson, R. G.: Intestinal Villi and Their Circulation in Relation to Absorption and Secretion of Fluid. Am. J. Physiol., 109: 387, 1934.
58. Magee, H. E., and Reid, E.: The Absorption of Glucose from the Alimentary Canal. J. Physiol., 73: 163, 1931.
59. Nasset, E. S., and Parry, A. A.: Passage of Fluid and Certain Dissolved Substances Through Intestinal Mucosa as Influenced by Changes in Hydrostatic Pressure. Am. J. Physiol., 109: 614, 1934.
60. Cori, C. F.: Rate of Absorption of a Mixture of Glucose and Galactose. Proc. Soc. Exp. Biol. Med., 23: 290, 1926.
61. Wilson, T. H., and Wiseman, G.: A Method for Studying Intestinal Metabolism and Absorption, J. Physiol., 121: 45P, 1953.
62. Wilson, T. H., and Vincent, T. H.: Absorption of Sugars In-vitro by the Intestine of the Golden Hamster. J. Biol. Chem., 216: 851, 1955.
63. Smyth, D. H., and Taylor, C. B.: Inhibition of Glucose Transport in the In-vitro Intestines by Phlorrhizin. J. Physiol., 130: 11P, 1955.
64. Jervis, E. L., Sheff, M. F., and Smyth, D. H.: Phlorrhizin Inhibition of Glucose Absorption In-vivo. J. Physiol., 131: 16P, 1956.
65. Laszt, L.: Z. Biochem., 276: 40, 1935. Cited by Verzan, F., and McDougall, E. J. (28).
66. Nakazawa, F.: Tohoku J. Exp. Med., 3: 288, 1922. Cited By Verzar, F., and McDougall, E. J. (28).
67. Lundsgaard, E.: Z. Biochem., 264: 209, 1933. Cited by Verzar, F., and McDougall, E. J. (28).
68. Laszt, L., and Süllmann, H.: Z. Biochem., 278: 401, 1935. Cited by Verzar, F., and McDougall, E. J. (28).
69. Beck, L. V.: Organic Phosphate and "Fructose" in Rat Intestinal Mucosa as Affected by Glucose and by Phlorrhizin. J. Biol. Chem., 143: 403, 1942.
70. Eiler, J. J., Stockholm, M., and Althausen, T. L.: The Effect of the Rate of Absorption of Glucose on the Phosphates in the Intestinal Mucosa. J. Biol. Chem., 134: 283, 1940.
71. Davidson, J. N., and Garry, R. C.: The Absorption of Monosaccharides from the Distal Small Intestine of Anaesthetized Cats. J. Physiol., 97: 509, 1940.
72. Hele, M. P.: The Phosphorylation and Absorption Sugars in the Rat. 2. Sugar Absorption In-vivo, and its Relationship to the Phosphorylation of Sugar In-vitro. Biochem. J., 55: 864, 1953.
73. Sols, A.: Phosphorylation of Sugars by the Intestinal Mucosa. Revista Espagnola de Fisiologia (Barcellona), 11: 277, 1955.
74. Newey, H., Smyth, D. H., and Whaler, B. C.: The Absorption of Glucose By the In-vitro Intestinal Preparation. J. Physiol., 129: 1, 1955.
75. Fridhandler, L., and Quastel, J. H.: Absorption of Sugars from Isolated Surviving Intestines. Arch. Biochem., 56: 412, 1955.
76. Abderhalden, E.: Z. Physiol. Chem., 78: 382, 1912. Cited by Verzar, F., and McDougall, E. J. (28).
77. Messerli, H.: Z. Biochem., 54: 446, 1913. Cited by Verzar, F., and McDougall, E. J. (28).
78. Oide, T.: Jap. J. Med. Sci. Trans., 1: 299, 1929. Cited by Verzar, F., and McDougall, E. J. (28).
79. Dent, C. E., and Schilling, J. A.: Studies on the Absorption of Proteins: The Amino acid pattern in the Portal Blood. Biochem, J., 44: 318, 1949.
80. Abderhalden, E. F., Frank, F., and Schittenhelm, A.: Z. Physiol. Chem., 63: 215, 1909. Cited by Verzar, F., and McDougall, E. J. (28).

81. Bolton, C., and Wright, G.: The Absorption of Amino-acids and their Distribution in the Body Fluids. J. Physiol., 89: 269, 1937.
82. Fridhandler, L., and Quastel, J. H.: Absorption of Amino-acids from Isolated Surviving Intestine. Arch. Biochem, 56: 424, 1955.
83. Kratzer, F. H.: Amino-acid Absorption and Utilization in the Chick. J. Biol. Chem., 153: 237, 1944.
84. Hober, R., and Hober, J.: Experiments on the Absorption of Organic Solutes in the Small Intestine of Rats. J. Cell. Comp. Physiol., 10: 401, 1937.
85. Scholfield, F. A., and Lewis, H. B.: A Comparative Study of the Metabolism of A-alanine, B-alanine, Serine and Isoserine; Absorption from the Gastrointestinal Tract. J. Biol. Chem., 168: 439, 1947.
86. Gibson, Q. H., and Wiseman, G.: Selective Absorption of Stereoisomers of Amino-Acids from Loops of Small Intestine of the Rat. Biochem. J., 48: 426, 1951.
87. Matthews, D. M., and Smyth, D. H.: Stereo Chemically Specific Absorption of Alanine from the Intestine Into the Blood Stream. J. Physiol., 116: 20P, 1952.
88. Clarke, E. W., Gibson, Q. H., Smyth, D. H., and Wiseman, G.: Selective Absorption of Amino-Acids from Thiry-Vella Loops. J. Physiol., 112: 46P, 1951.
89. Wilson, T. H., and Wiseman, G.: Metabolic Activity of the Small Intestine of the Rat and Golden Hamster. J. Physiol., 123: 126, 1954.
90. Wiseman, G.: Preferental Transference of Amino-Acids from Amino-Acid Mixtures by Sacs of Everted Small Intestine of the Golden Hamster. J. Physiol., 127: 414, 1955.
91. Kuroda, Y., and Gimbel, N. S.: Selective Disappearance of Stereoisomers of Amino Acids From the Human Small Intestine. J. Appl. Physiol., 7: 148, 1954.
92. Orten, A. U., and Johnston, C. G.: Comparative Absorption of Amino Acids from the Intestine. Fed. Proc., 12: 107, 1953.
93. Kamin, H., and Handler, P.: Effect of Presence of Other Amino Acids Upon Intestinal Absorption of Single Amino Acids in the Rat. Am. J. Physiol., 169: 305, 1952.
94. Tuba, J., and Dickie, N.: The Role of Alkaline Phosphate in Intestinal Absorption. IV. The Effects of Various Proteins on Levels of the Enzyme in Intestinal Mucosa. Can. J. Biochem. Physiol., 33: 89, 1955.
95. Code, C. F., Scholer, J. F., et. al.: Absorption of Water From the Upper Part of the Human Gastrointestinal Tract. Proc. Staff Meet. Mayo Clin., 29: 235, 1954.
96. Scholer, J. F., and Code, C. F.: Rate of Absorption of Water From Stomach and Small Bowel of Human Beings. Gastroenterology 27: 565, 1954.
97. Lee, P. R., Code, C. F., and Scholer, J. F.: The Influence of Varying Concentrations of NaCl on the Rate of Absorption of Water From the Stomach and Small Bowel of Human Beings. Gastroenterology, 29: 1008, 1955.
98. Blickenstaff, D. D.: Increase in Intestinal Absorption of Water From Isomotic Saline Following Pitressin Administration. Am. J. Physiol., 179: 471, 1954.
99. Blickenstaff, D. D.: Effect of Meraluride and of Mercuric Chloride on Intestinal Absorption of 0.9% NaCl Solution. Am. J. Physiol., 178: 371, 1954.
100. Höber, R.: Pflügers Arch., 74: 246, 1899. Cited by Verzar, F., and McDougall, E. J. (28).
101. Höber, R.: Pflügers Arch., 70: 624, 1898. Cited by Verzar, F., and McDougall, E. J. (28).
102. Höber, R.: Pflügers Arch., 94: 337, 1903. Cited by Verzar, F., and McDougall E. J. (28).
103. Norberg, B.: Pflügers Arch., 234: 200, 1934. Cited by Verzar, F., and McDougall, E. J. (28).
104. Frey, v. E.: Z. Biochem., 19: 509, 1909. Cited by Verzar, F., and McDougall, E. J. (28).
105. Goldschmidt, S., and Dayton, A. B.: Studies in the Mechanism of Absorption From the Intestine. Am. J. Physiol., 48: 433, 1919.

106. Burns, H. C., and Visscher, M. D.: The Influence of Various Anions on the Lyotropic Series Upon the Sodium and Chloride Content of Fluids in the Intestine. Am. J. Physiol., 110: 490, 1934.

107. Rolpke, R. R., and Visscher, M. B.: Osmotic Relationships Between Blood Plasma and Intestinal Fluid During Absorption. Proc. Soc. Exp. Biol. Med., 41: 500, 1939.

108. Visscher, M. B., Fetcher, E. S., Jr. et. al.: Isotopic Tracer Studies on the Movement of Water and Ions Between Intestinal Lumen and Blood. Am. J. Physiol., 142: 550, 1944.

109. Grim, E., Lee, J. S., and Visscher, M. B. Water Exchange between Intestinal Contents, Tissues and Blood. Am. J. Physiol., 182: 359, 1955.

110. Fisher, R B.: Absorption of Water and of Some Non-Electrolytes from the Surviving Small Intestine of the Rat. J. Physiol., 124: 21P, 1954.

111. Wells, H. S.: The Passage of Materials Through the Intestinal Wall I. The Relationship Between Intra-Intestinal Pressure and the Role of Absorption of Water. Am. J. Physiol., 99: 209, 1931.

112. Granick, S.: Iron Metabolism. Bul. N. Y. Acad. Med., 30: 81, 1954.

113. Hahn, P. F., Bale, W. F., Ross, J. F., Balfour, W. M., and Whipple, G. H.: Radioactive Iron Absorption by Gastrointestinal Tract; Influence of Anemia, Anoxia, and Antecedent Feeding Distribution in Growing Dogs. J. Exp. Med., 78: 169, 1943.

114. Granick, S.: Ferritin. IX. Increase of the Protein Apoferritin in the Gastrointestinal Mucosa as a Direct Response to Iron Feeding. The Function of Ferritin in the Regulation of Iron Absorption. J. Biol. Chem., 164: 737, 1946.

115. Moore, C. V., Arrowsmith, W. R., Welch, J., and Minnich, V.: Studies in Iron Transportation and Metabolisms; Observations on Absorption of Iron from the Gastrointestinal Tract. J. Clin. Invest., 18: 553, 1939.

116. Endicott, K. M., Gillman, T., Brecher, G., Ness, A. T., Clarke, F. A., and Adams, K. E. R.: A Study of Histochemical Iron Using Tracer Methods. J. Lab. and Clin. Med., 34: 414, 1949.

117. Everett, N. B., Garrett, W. E., and Simmons. B. S.: Lymphatics in Iron Absorption and Transport. Am. J. Physiol., 178: 45, 1954.

118. Taylor, J., Stivem, P., and Reid, E. W.: Experimental and Idiopathic Siderosis in Cats. J. Path. Bact., 41: 397, 1935.

119. Kinney, T. D., Finch, C. A., Kaufman, N., Hegsted, M., and Partington, P. F.: The Relationship of the Pancreas to the Absorption of Iron. Am. J. Path., 26: 746, 1950.

120. Kinney, T. D., Kaufman, N., and Klavins, J.: Effect of Ethionine-induced Pancreatic Damage on Iron Absorption. J. Exp. Med., 102: 151, 1955.

DISTURBANCES IN PROTEIN AND LIPID METABOLISM IN MALABSORPTION SYNDROME

DAVID ADLERSBERG, M.D.
CHUN I. WANG, M.D.
AND
ELAINE T. BOSSAK, M.D.
New York, N. Y.

The malabsorption syndrome (idiopathic sprue) is a complex metabolic disorder in which multiple defects of intestinal absorption form an integral part. Steatorrhea and emaciation are important clinical features. It has previously been established that the sprue syndrome is associated with hypoproteinemia and hypolipidemia (1–6). In a study of the characteristic features of this disorder in a selected group of 94 patients, several were encountered in whom isolated deficiencies of serum proteins and lipids suggested the presence of a more profound disturbance in protein and/or fat metabolism. In the majority of the patients data concerning serum proteins and serum lipid partition were collected during acute relapse and during periods of clinical control. A detailed presentation of these laboratory data, together with a correlation with clinical symptoms and therapy, was therefore undertaken. In addition, three illustrative cases are present in detail.

The group consisted of 32 men and 62 women whose age averaged 45 years. The mean duration of symptoms prior to first hospitalization was 7.2 years. The follow-up period averaged 5.2 years. A detailed study of the symptomatology and signs of these patients is presented elsewhere in this symposium (7).

SERUM PROTEINS IN THE MALABSORPTION SYNDROME

Determinations of serum proteins by the biuret method (8) were performed in 67 patients. The mean level was 5.7 gm. per cent (range 3.6 to 8.5). In 19.4 per cent of the cases the total protein concentration was below 5.0 gm. per cent. Serum albumin, determined by the same method in 60 patients, ranged from 1.4 to 5.3 gm. per cent with a mean concentration of 3.3. In 51.8 per cent of the cases the serum albumin level was below 3.5 gm. per cent. In 23.4 per cent the level was lower than 2.5 gm. per cent.

In 16 patients a considerable degree of dependent edema was present at the time of hospitalization. In this group the mean total protein concentration was decidedly lower, averaging 4.8 gm. per cent. Serum albumin levels were similarly depressed to an average of 2.4 gm. per cent. These findings suggest that edema in sprue is usually correlated with hypoproteinemia, in particular with hypoalbuminemia. Two of the 16 patients had ascites in addition to dependent edema; their total protein levels were 3.1 and 4.3 gm. per cent, while serum albumin concentrations were 1.7 and 1.9 gm. per cent.

From the Department of Medicine, The Mount Sinai Hospital, New York, N. Y.

The over-all depression of serum total proteins, including both albumin and globulin, suggests that there is impaired synthesis of these components. This may be a result of deficiency in precursors due to inadequate intake, impaired absorption of protein, loss in the stool, and impaired synthesis by the liver due to effects of malnutrition or as part of the general metabolic disorder. Serum albumin is affected to a greater degree than the globulins, as reflected by the more marked depression in levels of this protein fraction.

It is of interest that the levels of serum globulin in the total group of patients were the same as those with edema. In the former the average was 2.4 mg. per cent, while in the latter the average was 2.3. These levels are somewhat depressed, suggesting that there is an impairment of globulin formation in sprue. However, this is not necessarily correlated with the clinical severity of the sprue syndrome, is not responsible for the drop in total protein and is not correlated with edema.

A further investigation of the serum protein pattern and globulin distribution in patients with sprue was undertaken. Other investigators had described the occurrence of a sprue-like syndrome in patients with agammaglobulinemia (9)

TABLE I

Serum protein patterns in idiopathic sprue

Case No.	Sex	Age	Paper Electrophoresis					Chemical Analysis		
			Albumin	Globulins Alpha-1	Alpha-2	Beta	Gamma	Total Protein	Albumin	Globulin
			Per cent of total stainable protein					gm. per cent		
1	F	42	36.9	7.7	15.4	13.3	26.7	6.8	3.9	2.9
2	F	35	51.4	10.8	8.1	10.8	18.9	7.2	5.1	2.1
3	F	71	40.7	5.3	11.2	19.1	23.7	7.5	4.5	3.0
4	F	48	50.8	4.7	10.1	11.7	22.7	7.2	4.5	2.7
5	F	43	44.9	11.8	12.6	11.8	18.9	6.4	3.9	2.5
6	M	38	46.5	5.1	8.5	17.0	22.9	7.2	4.0	3.2
7	M	67	36.0	6.2	16.4	23.4	18.0	5.4	3.3	2.1
8	F	65	46.9	5.0	15.0	13.7	19.4	7.5	4.5	3.0
9	M	54	38.9	6.4	18.3	18.3	18.1	4.4	2.5	1.9
10	F	44	50.0	5.6	10.0	19.4	15.0	6.0	4.0	2.0
11	F	48	45.1	8.4	18.3	18.3	19.9	4.8	2.7	2.1
12	M	26	37.5	7.1	13.8	18.7	22.7	7.5	4.5	3.0
13	F	46	38.7	12.7	8.7	21.0	19.1	6.2	3.8	2.4
14	F	62	48.2	5.4	12.1	17.5	16.8	7.2	4.4	2.8
15	F	62	44.0	7.7	17.6	12.0	18.7	6.7	4.6	2.1
16	F	69	32.6	9.8	18.5	20.6	18.5	6.3	3.3	3.0
17	M	57	49.6	6.2	13.8	9.7	20.7	5.7	3.5	2.2
18	F	36	53.7	3.6	10.5	10.5	21.7	7.0	3.9	3.1
19	F	63	34.6	6.0	13.8	23.0	22.6	7.5	3.9	3.6
20	M	67	40.7	4.7	14.0	12.3	28.3	7.7	3.8	3.9
Mean..........			43.3	6.9	13.2	16.0	20.6	6.7	3.9	2.7
Normal			52.5	4.2	12.2	14.0	17.1	7.5	4.5	3.0
S.D. ±........			3.7	1.5	3.6	2.9	3.0			

Therefore, the sera of 20 patients with idiopathic sprue were subjected to paper electrophoresis using a method previously described (10).

A horizontal apparatus with free suspension of the paper strips was employed, using a Veronal buffer at p*H* 8.6, ionic strength 0.05. After application of 0.007 ml. of serum, a potential of 250 volts was applied for 6½ hours with a current of 2.5 milliamperes per strip. The paper strips were then stained with Amidoblack after drying at 70°C. The patterns were read in a photoelectric densitometer and the curves derived were evaluated planimetrically. Five components were determined: albumin, alpha-1, alpha-2, beta and gamma globulins. Simultaneously, total protein, albumin and globulin were determined chemically (biuret method).

The data from the individual patients is presented in Table I. Albumin levels were low, and those determined electrophoretically were even lower than those determined by the ordinary chemical method. The lowest levels were obtained in patients who were seriously ill. In this group of patients no instances of agammaglobulinemia were noted and generally gamma globulin was increased. There was also a tendency to increased levels of beta globulin which was marked in some instances. There was little change in levels of alpha-2 globulins and an increase in alpha-1 globulin. These apparently non-specific globulin alterations indicate that serum globulin levels are maintained at absolute levels which approximate those in normal sera, while serum albumin is below normal.

In one patient, on repeated examinations, electrophoresis of the serum yielded a spike in the gamma globulin region similar to that observed in patients with multiple myeloma. Bone marrow and roentgen examinations failed to yield evidence of any blood dyscrasia. No macroglobulins were present in the serum.

INTRACTABLE HYPOPROTEINEMIA AND EDEMA AS PROMINENT FEATURES OF IDIOPATHIC SPRUE

The following two patients, observed over a period of 12 and 17 years, respectively, are presented to illustrate hypoproteinemia and edema as leading clinical features of sprue.

Case 1

A 21 year old girl was hospitalized in 1932 because of progressive leg edema of five months duration. Six months before she had had a tonsillectomy which was followed by four or five post-operative hemorrhages. Shortly thereafter she developed anorexia, postprandial abdominal pain and weakness. On examination she appeared pale and her blood pressure was 102/50. There was pitting edema of the lower legs. The hemoglobin was 11.9 gm. per cent. Urinalysis was negative. The total protein was 5.2 gm. per cent with albumin 3.6 and globulin 1.6 gm. per cent. A diagnosis of static edema and psychoneurosis was made.

She was hospitalized eight months later with persistent edema and pain in the left flank and leg. An intravenous pyelogram was negative. The diagnosis of sacro-iliac arthritis was made.

She was hospitalized again in 1935 at age 24 years. In the interval she had intermittent ankle edema and fatigue. She also developed tetany, abdominal pain and diarrhea. She had been hospitalized elsewhere where pigmentation of the skin was noted. Hypoproteinemia (3.3 to 5.8 gm. per cent) persisted. Serum calcium level was 7 mg. per cent. Roentgen examination of the gastrointestinal tract was reported to be normal. She developed acute intestinal obstruction due to incarceration of a post-appendectomy ventral hernia which was repaired. Five weeks before admission severe diarrhea recurred with abdominal pain, vomiting, anorexia, progressive low grade fever, weakness and paresthesias. She was emaciated and pale. The abdomen was diffusely tender and doughy. There was free hydrochloric acid in the gastric contents. Total protein was 5.4 gm. per cent, albumin 3.1. The glucose tolerance curve was flat. Barium enema revealed redundancy of the sigmoid and dilatation of the colon. Following a barium meal there was patchy distribution in the small intestine. The patient improved but ambulation was followed by recurrence of edema. There were two episodes of tetany; serum calcium was 6.8 mg. per cent. She also developed glossitis. She was treated with a high protein diet, calcium and viosterol. Edema persisted and blood proteins remained 4.8 to 5.2 gm. per cent.

At this time the diagnosis of non-tropical sprue was suggested. She was treated with diet, liver extract, calcium and vitamins and thereafter she gained weight. The edema diminished but continued to recur. Bouts of diarrhea persisted and were accompanied by tetany and paresthesias.

She was hospitalized again eight years later (1943). She had lost 17 pounds during that period. The blood pressure was 90/68. There was no edema. Hemogram was normal. Total serum protein concentration was 4.3 gm. per cent and albumin was 2.3 gm. per cent. Serum calcium concentration was 6.3 mg. per cent. Duodenal drainage showed normal pancreatic enzymes. Vitamin A and glucose tolerance tests revealed flat curves. Fecal fat content was 21.4 per cent of dry weight. X-ray of the small intestine showed dilatation and segmentation. She received a high protein diet, plasma, amino acid infusions, vitamins and calcium. Total serum proteins rose to 5.8 gm. per cent and calcium concentration to 10 mg per cent. The diarrhea diminished.

She was hospitalized again four months later at age 33 years (1944) for diarhea, tetany, abdominal cramps and fever. Chvostek and Trousseau signs were present. Total serum proteins were 6.0 gm. per cent and the albumin was 3.6 gm. per cent. There was a prolonged Q-T interval in the electrocardiogram. She improved only temporarily on a regimen of diet, liver extract, vitamins and calcium. Symptoms persisted until her final admission four months later. She appeared emaciated (weight 91 pounds). There was moderate clubbing of the fingers. Microscopic examination of the stool revealed large amounts of fat. On roentgen examination there was marked dilatation of the small intestine with loss of mucosal pattern and segmentation. Serum albumin was 2.5 gm. per cent and globulin was 1.5 gm. per cent. Serum calcium concentration was 8 mg. per cent and alkaline phosphatase was 31 King-Armstrong units. Therapy included diet, liver extract, pancreatin, vitamins and calcium as well as plasma, whole blood and AT-10. Her course was steadily downhill. She died suddenly with tetanic convulsions one month after admission. Postmortem examination revealed thromboses of the dural sinus and cerebral veins, visceral atrophy, fatty liver and distention of the intestine (11).

Comment: A young woman had hypoproteinemia and edema which persisted over a period of years. Tetany and hypocalcemia were prominent clinical features. Diarrhea and evidence of malabsorption were subsequently present. Symptoms continued despite vigorous therapy. The patient died 12 years after the onset of the disorder.

Case 2

A 54 year old white man had leg edema of varying degree beginning at the age of 27 years (1930). He had repeated episodes of erysipelas and cellulitis involving one or both legs since 1938. He was hospitalized four times from 1938 to 1945. During this period, there was constant hypoproteinemia which was considered the cause of the persistent edema. The serum total proteins ranged from 3.1 to 5.5 gm. per cent, with serum albumin ranging from 2.2 to 3.8 gm. per cent and globulin 1.1 to 1.9 gm. per cent. No cause for the hypoproteinemia could be found despite extensive investigation. Roentgenologic study of the small intestine in 1938 revealed hypomotility and evidence of edema of the intestinal wall. There was radiographic evidence of numerous phleboliths and calcification of vessels of both legs. Extensive pulmonary infarction occurred in 1940 followed by a loculated left pleural effusion which persisted for ten years and produced extensive fibrosis.

In 1945, steatorrhea was noted with two to four semi-formed bowel movements daily. Absorption studies included a normal glucose tolerance test (fasting level of 95 mg. per cent, maximum elevation 150 mg. per cent), impaired vitamin A absorption (serum vitamin A rose from an initial level of 51 μg. per cent to 72 at four hours) and markedly impaired glycine absorption. These defects of absorption were attributed to edema of the small intestine secondary to hypoproteinemia. He was treated with a high-protein, low-fat, low-salt diet, liver extract and vitamin B_{12} without improvement in hypoproteinemia and edema. He was under observation in the Nutrition Clinic for these features and was ultimately considered to be a case of idiopathic sprue resistant to conventional dietary and drug therapy. He was rehospitalized for institution of steroid therapy in 1951. Re-evaluation of his status revealed a chronically ill man with massive edema of both lower extremities simulating the picture of elephantiasis. There was swelling of the scrotum and slight pitting edema of the lower abdominal wall. Several areas of red, warm, slightly tender and indurated skin were present over the legs. The left chest was markedly contrasted with minimal expansion and scoliosis of the spine was present. Laboratory data revealed normal blood counts, normal minerals and electrolytes. The serum total proteins were 4.6 gm. per cent, with albumin 2.5 and globulin 2.1 gm. per cent. Roentgenologic study of the small intestinal showed thickening of mucosal folds, especially in the jejunum, interpreted as a "deficiency pattern". There was moderate generalized demineralization of the entire skeletal system and marked calcification of the arteries in the pelvis and the legs. Steatorrhea with fecal fat accounting for 30 to 40 per cent of the dry weight was present on repeated examinations despite the absence of diarrhea.

Corticotropin in daily doses of 60 to 100 mg. given for five weeks in the hospital failed to raise the serum proteins. Similarly, cortisone in daily doses of 80 to 100 mg., hydrocortisone 80 mg. and finally prednisone 40 mg. given in repeated trials between 1951 and 1956 produced no beneficial effects. The edema and hypoproteinemia persisted. Vitamin A absorption was impaired on repeated studies. The fasting serum vitamin A level averaged 40 μg. per cent and rose to a maximum of 49. The serum carotene level was also low (15 to 24 μg. per cent). The last roentgenologic study of the small bowel performed in 1956 revealed pseudodiverticulum of the jejunum, dilatation and increased secretion of the small bowel. Paper electrophoretic study of serum proteins showed marked depression of albumin and relative elevation of alpha-2 and beta globulin fractions (Table I, Case 9).

Comment: A 54 year old white man had intractable dependent edema due to hypoproteinemia for 27 years. The diagnosis of sprue was not made for 21 years. Steatorrhea, as well as mild diarrhea, malabsorption of protein and fats, and a slowly progressive deficiency pattern on roentgen examination of the small intestine was then noted. His course was further complicated by repeated episodes of phlebitis of the edematous legs and pulmonary infarction.

This case shows that chronic intractable edema and hypoproteinemia may be the outstanding clinical feature of the sprue syndrome even in the absence of severe manifestations of the disorder. This also illustrates the occurrence of selective dissociation of degrees of malabsorption of various substances and perhaps differences in the intensity of metabolic defects in sprue.

SERUM CHOLESTEROL, PHOSPHOLIPIDS AND TOTAL LIPIDS

Serum total and free cholesterol was determined by the Sperry-Schoenheimer method (12), phospholipids by Sperry's modification of the Fiske-SubbaRow method (13) and total lipids by the gravimetric method of Bloor (14). The determinations were performed on serum drawn in the fasting state.

Serum cholesterol determinations were performed in 76 patients with active sprue; phospholipids and total lipids, in 42 patients. Since serum cholesterol and phospholipid concentrations vary normally with age and sex (15) the levels of these lipids in sprue patients were separated accordingly (Figs. 1 and 2). For purposes of comparison, the average serum lipid concentrations in normal men and women were used. These were obtained from a survey performed previously in this laboratory from a 1200 person segment of the population of New York City (16).

Serum cholesterol concentration in the entire group of patients averaged 162 mg. per cent. Thirty-six (47.4 per cent) had serum cholesterol levels below 150;

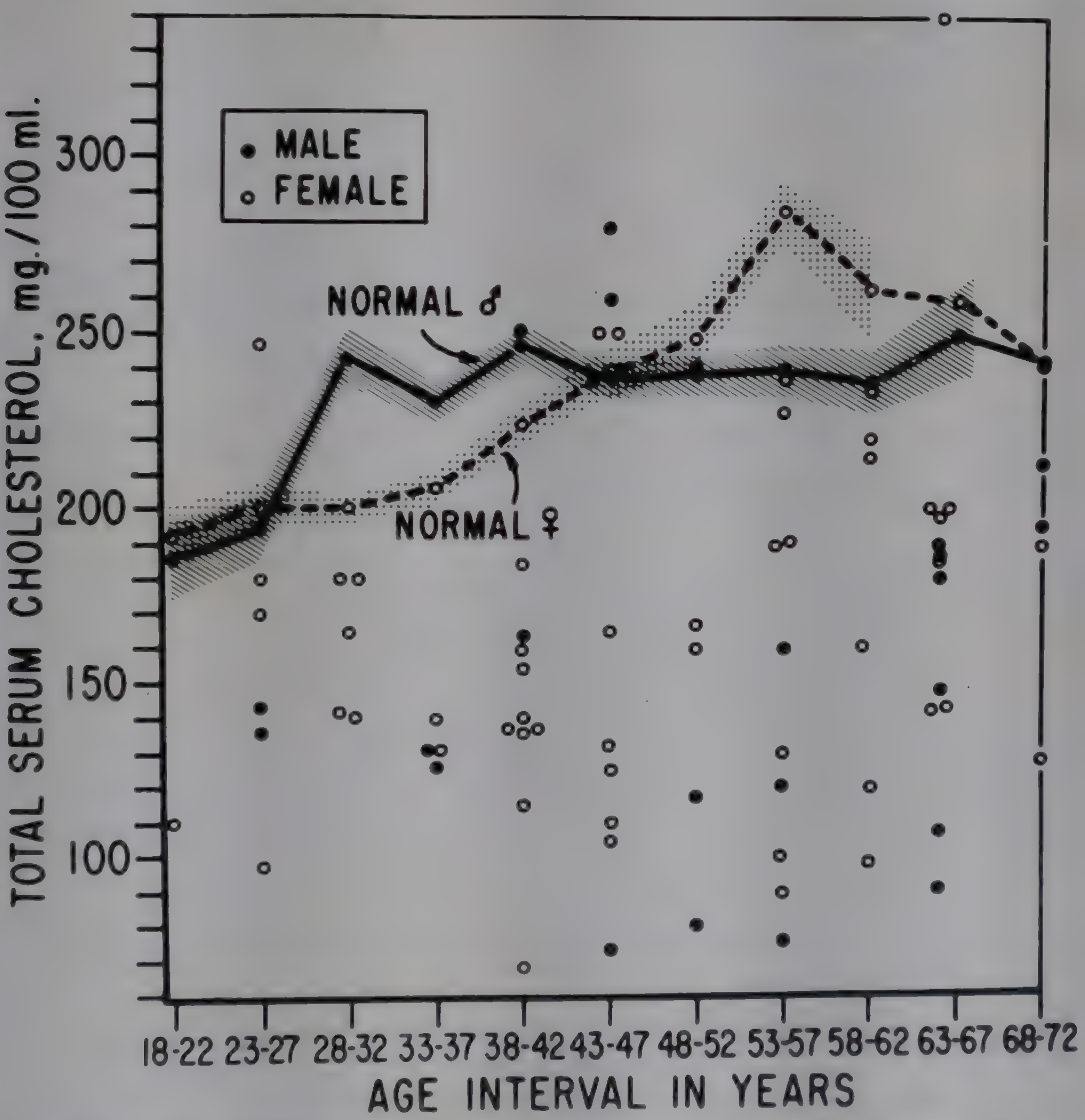


FIG. 1. Individual determinations of serum total cholesterol in 76 patients with idiopathic sprue separated according to age and sex. The curves represent the mean cholesterol levels obtained in healthy male and female controls at the various ages (16). The shaded areas represent one standard deviation from the mean.

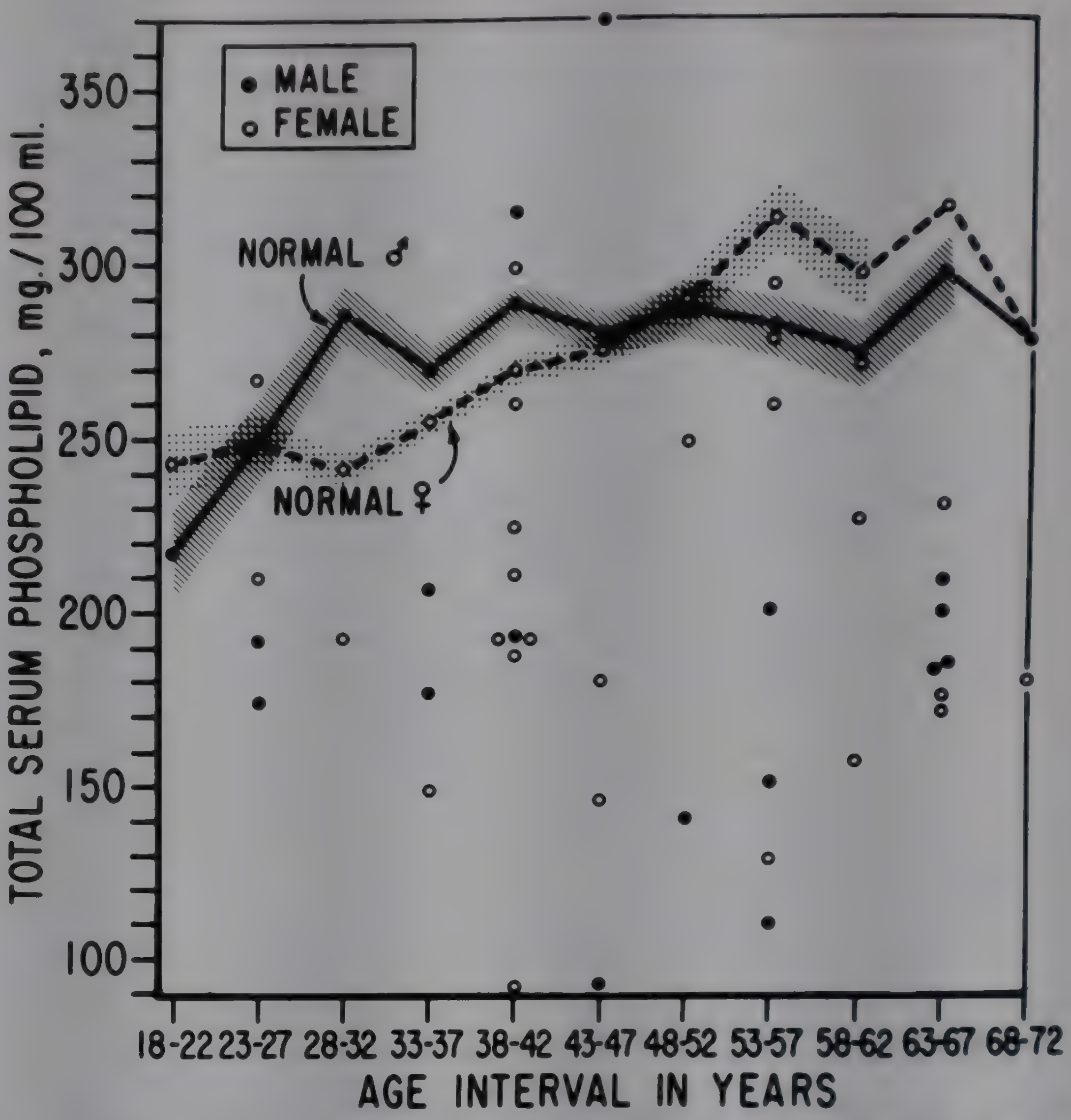


FIG. 2. Individual determinations of serum phospholipids in 42 patients with idiopathic sprue separated according to age and sex. The curves represent the mean phospholipid levels obtained in healthy male and female controls at the various ages (16). The shaded areas represent one standard deviation from the mean.

the lowest level was 68 mg. per cent. The low serum cholesterol levels were found mostly in patients who had been chronically ill for a long time or in acute crisis of active sprue. A graph of the individual determinations at various age levels, compared to the normal curve, showed that 88 per cent were lower than one standard deviation below the normal mean and 2.6 per cent were within one standard deviation (Fig. 1). In 9.4 per cent the values were greater than one standard deviation above the normal mean. These patients could be instances of idiopathic hypercholesteremia associated with sprue. There was no correlation between cholesterol levels, age and sex. The percentage of esterified cholesterol remained normal (75 per cent).

The average serum phospholipid concentration was 203 mg. per cent. The lowest level was 92 mg. per cent. Twenty-three patients (55 per cent) had levels below 200 mg. per cent. The lower levels of phospholipids were obtained in patients who had similar depression of cholesterol. Individual determinations are presented in Figure 2. Total lipid levels averaged 584 mg. per cent; 40.5 per cent of cases studied were below 500 mg. per cent. This serum lipid fraction was less depressed than either cholesterol or phospholipids.

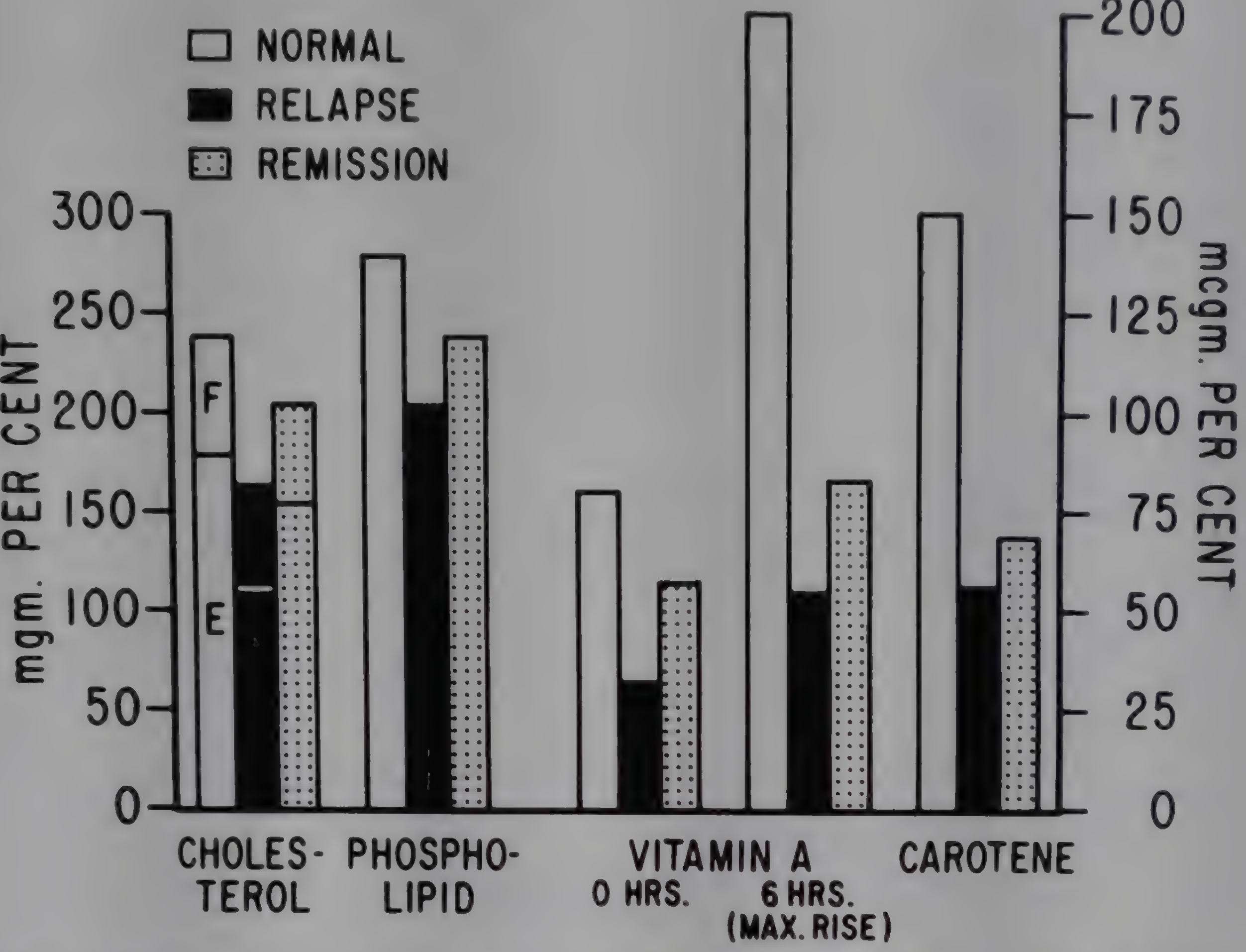


FIG. 3. Comparison of levels of serum cholesterol, phospholipids, "fasting" vitamin A, vitamin A six hours after oral administration of the vitamin, and carotene in patients with sprue in remission and relapse and in normal individuals. F = free cholesterol, E = esterified cholesterol.

In 29 patients serial study of serum lipid partition was performed during periods of therapy-induced clinical control. Levels of all lipid fractions were increased, but still remained below the healthy control levels (Fig. 3). Cholesterol levels were 203 mg. per cent (relapse, 162; control, 238). Phospholipids rose to 238 mg. per cent (relapse, 203; control, 278). Total lipids averaged 700 mg. per cent (relapse, 584; control, 700). Therefore, even in instances of full clinical control, some lipid levels remained depressed. This is illustrated by Figure 4 which depicts the clinical course and serum lipid levels of a typical patient with long-standing sprue who was followed during therapy with various adrenal cortical steroids.

Case 3

A 59 year old man with known idiopathic sprue for 27 years was hospitalized repeatedly for acute exacerbations of the disease as well as severe muscle and skin hemorrhages due to hypoprothrombinemia (17), possible subacute combined degeneration of posterior and lateral columns of the spinal cord (18), and marked generalized osteoporosis (osteomalacia) with fatigue fracture of the femoral neck (19). Because of the resistance to conventional dietary and anti-anemic therapy over a nine-year period, steroid therapy was instituted and resulted in clinical control during the last 5½ years. The maintenance dose was 12.5 mg. for cortisone and 15 mg. for hydrocortisone free alcohol. At present he is controlled on 10 mg. of prednisolone daily. During this period there was a decrease in number of bowel movements and gain in weight, with return to full activity, as the various steroids were ad

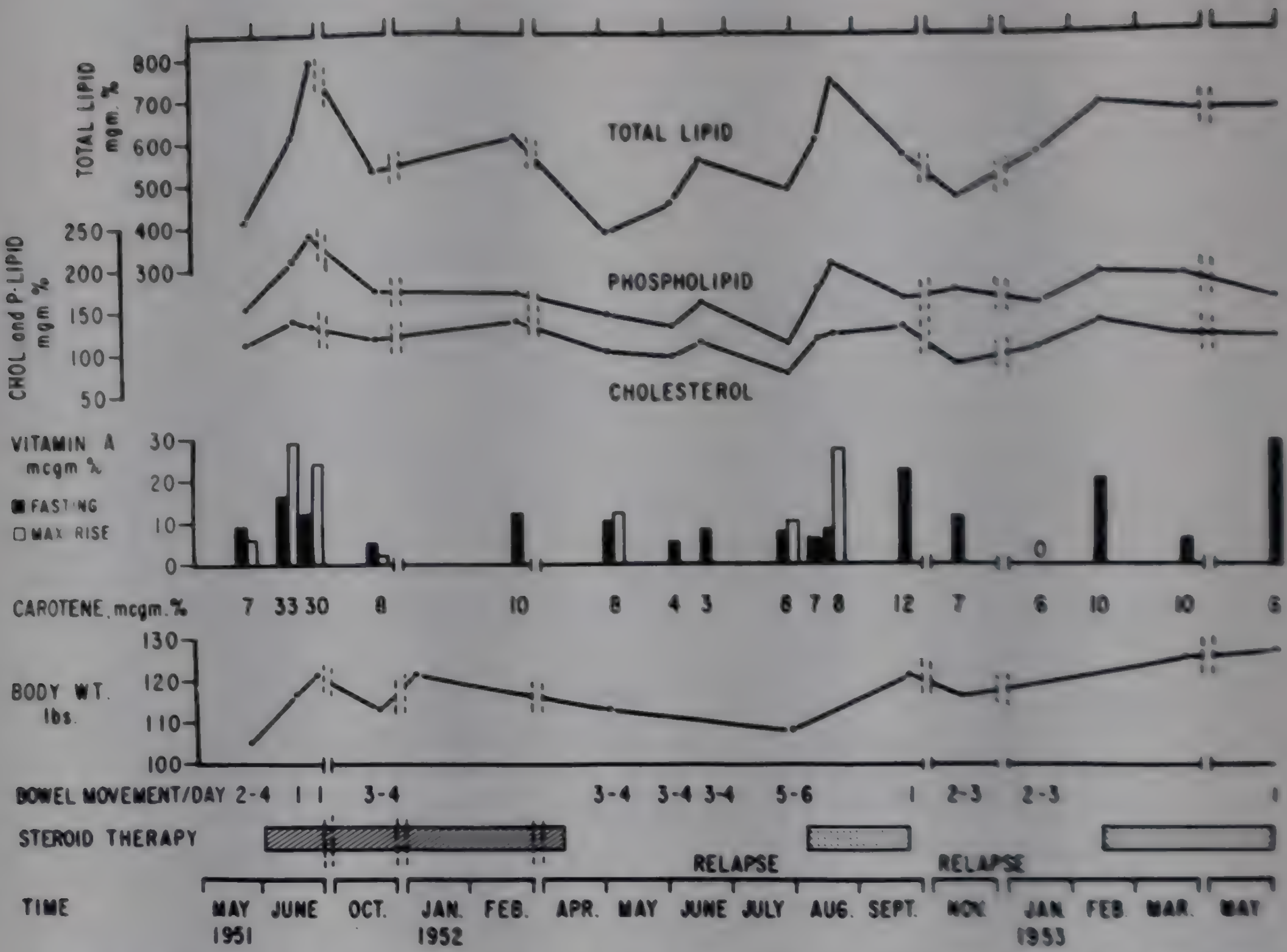


FIG. 4. Case 3, a 59-year old man with long-standing idiopathic sprue whose symptoms were controlled by treatment with a variety of steroids over a period of three years, two of which are presented in this graph. Attempts to withdraw these agents resulted in relapses. Variations in serum lipid fractions are correlated to changes in absorption of vitamin A and levels of serum carotene and to the clinical status of the patient. Response to therapy is indicated by gain in body weight and diminution in number of bowel movements daily. The three courses of steroid therapy consisted of cortisone (June 1951 to April 1952), hydrocortisone (August to September 1952) and hydrocortisone (February to May 1953).

ministered. However, serum lipid, vitamin A and carotene levels remained persistently low. Attempts to withdraw steroids resulted on three occasions in clinical relapse.

While there was an increase in concentration of serum lipids in association with good response to therapy in this and other patients, these levels were still markedly depressed. It is known that there is an increase in serum lipid levels under the influence of large doses of adrenal cortical steroids (20). Sprue patients under therapy receive a minimal maintenance dose of steroids which is therefore not the factor responsible for the lipid elevations. Rather, these may be a reflection of increased absorption, gain in weight and general clinical improvement as a result of therapy.

VITAMIN A TOLERANCE TEST AND SERUM CAROTENE LEVELS

Vitamin A absorption tests were performed following the oral administration of 180,000 i.u. of vitamin A in oil (3 ml. of Oleum Percomorpheum, Mead-Johnson). Serum vitamin A levels were analyzed by the micromethod of Bessey, et al. (21). The fasting levels of vitamin A obtained by this method ranged from 60 to 100 μg. per cent in healthy persons (22). In ten normal persons determina-

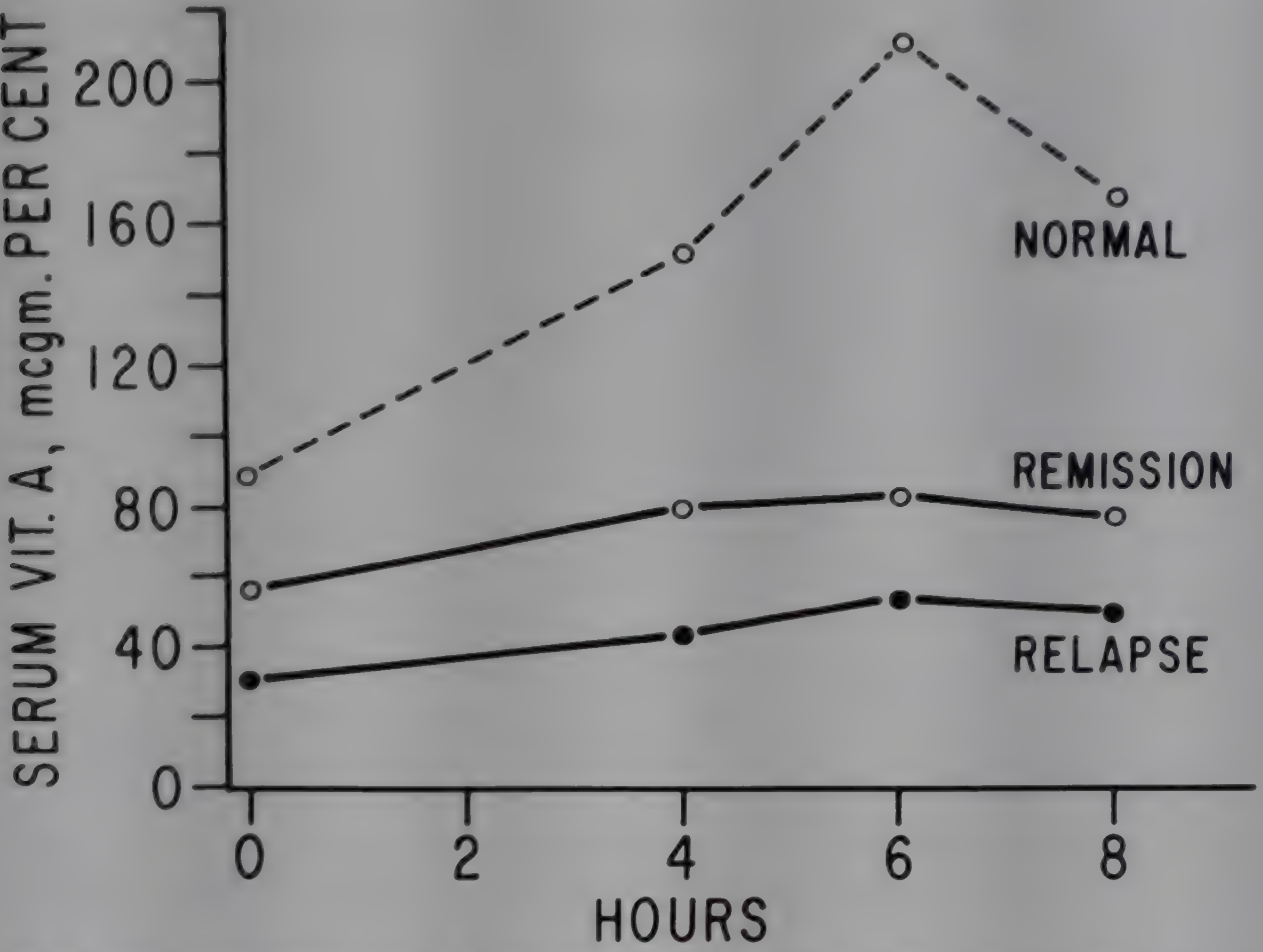


FIG. 5. The average vitamin A tolerance curve obtained in 54 patients with sprue in relapse compared with 29 sprue patients under clinical control. The normal absorption curve was the average of values obtained in ten healthy individuals.

tions were performed in the fasting state and four, six and eight hours after the vitamin A administration. The average values at fasting, four, six and eight hours were 87.0, 151.2, 210.1, and 167.9 μg. per cent, respectively (Fig. 5). The maximum rise occurred six hours after the ingestion of vitamin A and amounted to 123.1 μg. per cent over the fasting level. The occurrence of peak levels five to six hours after the test dose has been noted by others (23–25).

Of the group of 94 patients with idiopathic sprue in relapse, vitamin A absorption tests were done in 54. The serum vitamin A concentration in the fasting state averaged 31.3 μg. per cent (range 0 to 124). In 91 per cent the level was below 60 μg. per cent. In four patients low normal values were obtained. One patient had a moderately high fasting level (124 μg. per cent).

The absorption of vitamin A in the 54 patients with idiopathic sprue was considerably impaired (Fig. 5). The average values four, six and eight hours after the test dose were 43.2, 53.5 and 49.2 μg. per cent, respectively. The maximum rise occurred at six hours and amounted to an increase of 22.2 μg. above the average fasting level. Eight patients (14.8 per cent) showed no absorption of vitamin A during the eight hour test period. In these patients the serum vitamin A after vitamin A intake was either unchanged or lower than the initial level. Fifteen patients (27.8 per cent) had a maximum rise of less than 10 μg. per cent above the fasting level; 12 (21.8 per cent), less than 20 μg. per cent; 13 (23.6 per cent), less than 60 μg. per cent and 7 (12.8 per cent), less than 120 μg. per cent. In none of the patients did the maximum rise of serum vitamin A exceed 120 μg.

In six patients, the maximum rise of serum vitamin A was delayed and occurred eight hours after the oral administration of the vitamin. These patients usually showed negligible absorption of vitamin A in the first four to six hours. The average values of serum vitamin A in this group of patients were 39.3, 42.3, 47.3 and 61 μg. per cent at fasting, four, six and eight hours, respectively.

In 29 patients, repeated vitamin A tolerance tests were performed during the stages of relapse and remission. The fasting serum vitamin A level was found to be higher during remission in all patients (57.0 μg. per cent). During remission the average levels four, six and eight hours after vitamin A administration were 79.0, 82.0 and 77.3 μg. per cent, respectively. The mean maximum rise of serum vitamin A six hours after the oral test dose was 25.0 μg. per cent. As shown in Figure 6, the entire absorption curve during remission was on a higher level than during relapse, but the rate of absorption was probably not altered.

The serum carotene level averaged 56.3 μg. per cent in the same group of 54 patients in relapse. This level was considerably lower than values seen in normal persons (100 to 200 μg. per cent). In two patients, serum carotene was undeterminable; in 25 (45.5 per cent), the level was below 20 μg. per cent (Fig. 6). In only five of the 55 patients (9.1 per cent) was the serum carotene level

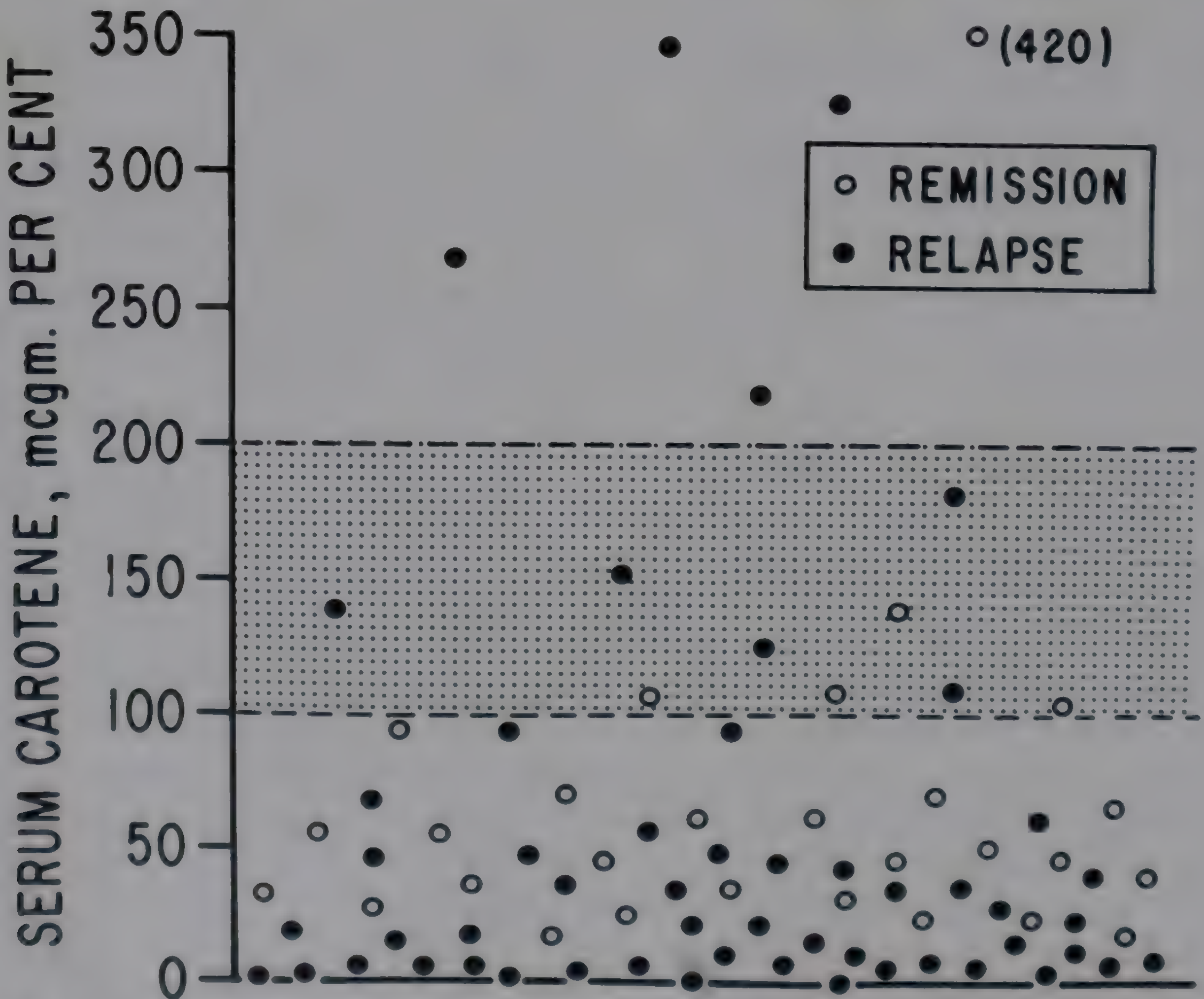


Fig. 6. Individual serum carotene levels in 54 patients with idiopathic sprue in relapse compared with 28 sprue patients under clinical control. The shaded area represents the range of normal serum carotene concentration.

within normal limits during relapse. All five were clinically milder instances of sprue. Their average fasting vitamin A level was also normal (69 μg. per cent). The normal serum carotene level in these patients may be interpreted as indicative of adequate carotene absorption. The latter was associated with a slightly impaired vitamin A absorption. Five other patients (9.1 per cent) had high serum carotene levels of 218, 268, 325, 346, and 347 μg. per cent, respectively. These five patients were also milder cases of sprue. Their serum vitamin A levels averaged 47.4 μg. per cent in the fasting state and rose to an average of 110.4 μg. per cent after the administration of vitamin A. This suggests that the presence of carotenemia may coincide with apparently normal vitamin A absorption in patients with sprue.

In 28 patients the serum carotene concentration was determined during remission. The average value for the group was 70.7 μg. per cent. The majority, 15 patients or 56.5 per cent, showed levels between 20 and 60 μg. per cent. In three patients, the serum levels became normal during remission, ranging from 104 to 117 μg. per cent. One patient who had a normal value during relapse became hypercarotenemic during remission (420 μg. per cent). This patient had a serum cholesterol level of over 300 mg. per cent on repeated examinations and is probably a member of a family with idiopathic hypercholesteremia. Thus, one may expect that these patients would have normal serum lipid, vitamin A and carotene levels with active sprue in relapse which then return to their originally high values during remission.

DISCUSSION

Hypoproteinemia and especially hypoalbuminemia is a constant feature of the full-blown sprue syndrome and is frequently associated with evidences of water retention such as edema, and at times ascites (4). Low levels of both serum albumin and globulin have been observed in large series of sprue patients; edema occurred when the total protein fell below 5 gm. per cent (6).

In the present group there was good correlation between levels of serum proteins (albumin) and the appearance of edema. On the other hand, Cooke, Peeney and Hawkins could find no correlation between edema and the level of the serum proteins in reviewing 100 patients with idiopathic steatorrhea (5). In two of their patients edema coincided with severe anemia, a finding which was not prominent among our patients. Comparison of the two series (The Mount Sinai Hospital in New York and the General Hospital in Birmingham, England) reveals a higher incidence of hypoproteinemia (19 per cent versus 7 per cent) and particularly of hypoalbuminemia (52 per cent versus 40 per cent) in our series. This may be a reflection of the more severe character of the sprue syndrome encountered in our group of patients.

None of the patients examined were found to exhibit the syndrome of agammaglobulinemia, recurrent infections and sprue, as has been reported (9). No characteristic pattern of alteration in serum globulins could be established by paper electrophoresis in the present group of patients although a variety of changes were observed.

The findings of depressed levels of serum lipids in patients with active sprue are in accordance with previous observations on this subject (1–3, 5). Keele demonstrated that fat absorption may remain below normal during remissions induced by liver extract (26). It is of interest that the serum lipid levels remained depressed in some patients even under good clinical control. This suggests that malabsorption is probably not the sole responsible factor and implies other as yet undetermined metabolic defects concerning lipid synthesis (3).

Malabsorption of fat-soluble vitamins is one of the conspicuous features of the idiopathic sprue syndrome. The absorption of vitamin A and carotene has been used by many investigators as a diagnostic test for this disorder (22, 24, 27, 28). Similarly, impaired absorption of vitamin E is probably responsible for the low serum levels of this vitamin in sprue (29).

In patients in full clinical remission serum vitamin A levels are often higher than in patients in relapse. The improved absorption can be detected only occasionally during the short eight-hour period of the absorption tests. The "tolerance curves" usually remain flat. This indicates that increased absorption of vitamin A over a prolonged period of time must occur to produce the increment in serum vitamin A. Correlation of fat balance studies with vitamin A tolerance test showed that the vitamin A tolerance curve became flat when fat absorption fell below 75 per cent (24).

Pretreating sprue patients with large doses of vitamin A for several days prior to performing a vitamin A tolerance test resulted in elevation of the serum levels of the vitamin but the "tolerance curves" remained flat indicating malabsorption (27, 30). This observation suggests that absorption of vitamin A is not directly correlated with the "fasting" serum level.

While patients presenting the classical clinical symptoms and signs of idiopathic sprue can be easily recognized, the clinical variants of incomplete sprue are usually diagnostic problems (7, 31). Hypoproteinemia, probably caused by malabsorption of protein as well as impaired synthesis, can be a presenting symptom. Case 1 illustrates that severe hypoproteinemia and edema can persist for years before appearance of the more classical and severe symptoms of diarrhea, tetany and hypocalcemia. Case 2 shows that massive intractable leg edema and repeated episodes of erysipelas, cellulitis and phlebitis may be associated with a mild form of the disorder.

In other patients, clinical features of malabsorption of lipids and fat-soluble vitamins predominate. Many patients present hemorrhagic manifestations resulting from malabsorption of vitamin K as the chief clinical feature of idiopathic sprue (17). Steatorrhea may be overlooked in the absence of diarrhea Case 3 illustrates persistent low levels of serum cholesterol, phospho-lipids, total lipids, vitamin A and carotene even under full clinical control in a patient with long-standing classical sprue observed over a period of many years. The serum vitamin A and carotene diminished to undeterminable levels during relapse. Hemorrhagic phenomena and osteomalacia in this patient were clinical manifestations of concomitant deficiencies in vitamins K and D.

Thus, pronounced defects in the serum levels and in the turnover of proteins and lipids represent an essential part of the metabolic derangement observed in the malabsorption syndrome. Other facets of this metabolic disturbance are alterations in the metabolism of water, iron, calcium, phosphorus, sodium and potassium. Additional discussions of these aspects are presented in other parts of the symposium (17, 32, 33).

SUMMARY

Patients with idiopathic sprue may present profound alteration of serum proteins and lipids as outstanding features of the disorder.

Study of serum total proteins, albumin and globulin in 67 patients with active sprue revealed low values which were correlated in 16 patients with the presence of edema. In 20 patients, sera were further fractionated by paper electrophoresis. Non-specific alterations in serum globulins were generally noted. In two patients (Cases 1 and 2), the clinical course of the sprue syndrome was characterized by protracted edema and hypoproteinemia as early manifestations of the disorder.

Serum cholesterol concentration studied in 76 patients and phospholipids and total lipid determined in 42 patients with active sprue yielded low levels. In 29 patients under clinical control, levels of lipid fractions increased but still remained low in many instances. This is illustrated by Case 3 who showed persistently depressed levels of all lipid fractions, despite good clinical control and evidence of improved absorption.

Vitamin A and carotene levels were low in 54 patients with active sprue and absorption of the vitamin was considerably impaired. While in 29 patients under good clinical control serum levels of vitamin A and carotene were higher, the absorption curves of vitamin A remained flat.

These observations suggest that disturbances in the metabolism of proteins and lipids are not always related to malabsorption *per se*.

REFERENCES

1. THAYSEN, T. E. H.: Ten Cases of Idiopathic Steatorrhea. Quart J. Med., 4: 359, 1935.
2. MASON-BAHR, P.: The Dysenteric Disorders. 2nd Ed. Williams and Wilkins Co. Baltimore, Md. 1943.
3. FRAZER, A. C.: Fat Metabolism and the Sprue Syndrome. Brit. Med. Jour., 2: 769, 1949.
4. LOPEZ, G. C., MILANES, F., SPIES, T. D., TOCA, R. L., ARAMBURU, T., AND LOPEZ, H.: The Association of Hypoproteinemia with Severe Tropical Sprue. Am. J. Med. Sci., 218: 660, 1949.
5. COOKE, W. T., PEENEY, A. L. P., AND HAWKINS, C. F.: Symptoms, Signs and Diagnostic Features of Idiopathic Steatorrhea. Quart. J. Med., 22: 59, 1953.
6. RODRIGUEZ-MOLINA, R.: Fundamental Concepts in the Diagnosis of Spruc. Ann. Int. Med., 40: 33, 1954.
7. BOSSAK, E. T., WANG, C. I,. AND ADLERSBERG, D.: Clinical Aspects of Malabsorption Syndrome. This volume, page 112.
8. GOA, J.: A Microbiuret Method for Protein Determination. Scandinav. J. Clin. & Lab. Invest., 5: 218, 1953.
9. SANFORD, J. P., FAVOUR, C. P., AND TUBEMAN, M. S.: Absence of Serum Gamma Globulins in an Adult. New Eng. J. Med., 250: 1027, 1954.
10. BOSSAK, E. T., WANG, C. I., AND ADLERSBERG, D.: Comparative Studies of Lipoproteins in Various Species by Paper Electrophoresis. Proc. Soc. Exper. Biol. & Med., 87: 637, 1954.

11. Himes, H. W., and Adlersberg, D.: Pathologic Studies in the Malabsorption Syndrome (Idiopathic Sprue). This volume, page 77.
12. Sperry, W. M., and Webb, M.: A Revision of the Schoenheimer-Sperry Method for Cholesterol Determination. J. Biol. Chem., 187: 97, 1950.
13. Sperry, W. M.: Electrophotometric Micro-determination of Phosphorus in Lipid Extracts. Indust. & Engin. Chem. (Analyt. ed), 14: 88, 1942.
14. Bloor, W. R.: Studies on Blood Fat. 1. Variations in the Fat Content of the Blood under Approximately Normal Conditions. J. Biol. Chem., 19: 1, 1914.
15. Keys, A., Mickelsen, O., Miller, E. O., Hayes, E. R., and Todd, R. L.: The Concentration of Cholesterol in Blood Serum of Normal Man and Its Relation to Age. J. Clin. Invest., 29: 1347, 1950.
16. Adlersberg, D., Schaefer, L. E., Steinberg, A. G., and Wang, C. I.: Age, Sex, Serum Lipids and Coronary Atherosclerosis. J. A. M. A., 162: 619, 1956.
17. Wang, C. I., and Bossak, E. T.: Hemorrhagic Manifestations in Idiopathic Sprue: A report of 25 Cases and Review of Literature. This volume, page 143.
18. Sencer, W.: Neurological Manifestations in the Malabsorption Syndrome. This volume, page 157.
19. Hartley, J.: Osseous Changes and Fractures in Malabsorption Syndrome. This volume, page 172.
20. Adlersberg, D., Schaefer, L. E., and Drachman, S. R.: Development of Hypercholesteremia during Cortisone and ACTH Therapy. J. A. M. A., 144: 909, 1950.
21. Bessey, O. A., Lowry, O. H., Brock, M. J., and Lopez, J. A.: The Determination of Vitamin A and Carotene in Small Quantities of Blood Serum. J. Biol. Chem., 166: 177, 1946.
22. Adlersberg, D., Sobotka, H., and Bogetin, B.: Effect of Liver Disease on Vitamin A Metabolism. Gastroenterology, 4: 164, 1945.
23. Ingelfinger, F. J.: The Diagnosis of Sprue in Non-tropical Areas. New Eng. J. Med., 228: 180, 1943.
24. Legerton, Jr., C. W., Texter, Jr., E. C., and Ruffin, J. M.: Observations in the Vitamin A Tolerance Curve as an Index of the Degree of Fat Absorption. Gastroenterology, 23: 477, 1953.
25. Anderson, D. H., and DiSant'Agnese, P. A.: Idiopathic Celiac Disease. 1. Mode of Onset and Diagnosis. Pediatrics, 11: 207, 1953.
26. Keele, K. D.: A Study of the Onset and Cyclic Development of the Sprue Syndrome. Brit. Med. Jour., 2: 111, 1946.
27. Patterson, J. C. S., and Wiggins, H. S.: An Estimation of Plasma Vitamin A and the Vitamin A Absorption Test. J. Clin. Path., 7: 56, 1954.
28. Patterson, J. C. S.: The Sprue Syndrome. Am. J. Med. Sci., 231: 92, 1956.
29. Darby, W. J., Cherrington, M. E., and Ruffin, J. M.: Plasma Tocopheral Levels in Sprue. Proc. Soc. Exper. Biol. & Med., 63: 310, 1946.
30. Popper, H., Steigman, F., and Zevins, S.: On the Variations of the Plasma Vitamin A Level after the Administration of Large Doses of Vitamin A in Liver Disease. J. Clin. Invest., 22: 775, 1943.
31. Adlersberg, D., and Schein, J.: Clinical and Pathological Studies in Sprue. J.A.M.A., 134: 1459, 1947.
32. Cooke, W. T.: Water and Electrolyte Upsets in the Steatorrhea Syndrome. This volume, page 47.
33. Estren, S.: The Blood and Bone Marrow in Idiopathic Sprue. This volume, page 130.

WATER AND ELECTROLYTE UPSETS IN THE STEATORRHEA SYNDROME

W. TREVOR COOKE, M.D., F.R.C.P.

It has become increasingly evident that any disorder which is associated with diarrhea may manifest the clinical signs of electrolyte depletion; it has not been as widely recognised that conditions affecting the intestine in which diarrhea is not necessarily a prominent feature also provide similar upsets. The normal subject passes 100–200 ml. of water per day in his stools and 2–5 mEq. Na and 10–15 mEq. K. Increase in the amount of water in the stools, as for example in any patient with diarrhea, is associated with an increase in the excretion of sodium, so that there appears to be a direct relation between the two. The amounts of sodium that may be found in severe diarrheas may be as much as 200–250 mEq. per day. In patients suffering from non-tropical sprue it has been found that there is an increased fecal excretion of potassium, even in formed stools when the water content is less than 250 ml. per day. In such instances, the daily excretion of potassium is around 25 mEq. though on occasions as much as 60 mEq. may be found. With an increase of the fluid content, the amount of potassium stays relatively unchanged until large quantities of water are being passed. The potassium excreted then increases to help maintain the isotonicity of the colonic contents. Even so, the amounts of potassium in the stools do not usually exceed 100 mEq. (1) (Figure 1). The reasons for this increased excretion of potassium in the stools of patients with steatorrhea are not readily apparent. It appears to be entirely endogenous in origin for the administration of large amounts of potassium by mouth does not lead to any significant increase in the feces and of a dose of K^{42} given intravenously, 20 per cent is excreted in the feces and 80 per cent in the urine.

In addition to the upsets in the fecal excretion of water and electrolytes, many patients with steatorrhea show upsets in urinary excretion of water, as evidenced by a marked nocturnal polyuria. This manifestation appears when the patients are in relapse and usually clears up completely when the patients are well. It can be the most troublesome symptom, causing the patient to rise 4 or 5 times per night to pass urine. Even on a daily intake of 12–1400 ml., urine volumes as high as 4 ml. per minute may be passed between 12 midnight and 1 a.m. There is no evidence that this is caused by an electrolyte diuresis, but rather it appears to be an inversion of the normal diurnal rhythm, whatever the physiological cause for this may be. Wollaeger and Scribner drew attention to the poor diuresis that follows oral ingestion of water in patients with the severe form of the disorder (2). They suggested that the nocturnal diuresis was related to the retention of large volumes of water in the small intestine during the abnormally prolonged period necessary for digestion and absorption of food. They demonstrated clearly that the diuresis could not be accounted for by the difference in

From the General Hospital, Birmingham, England.

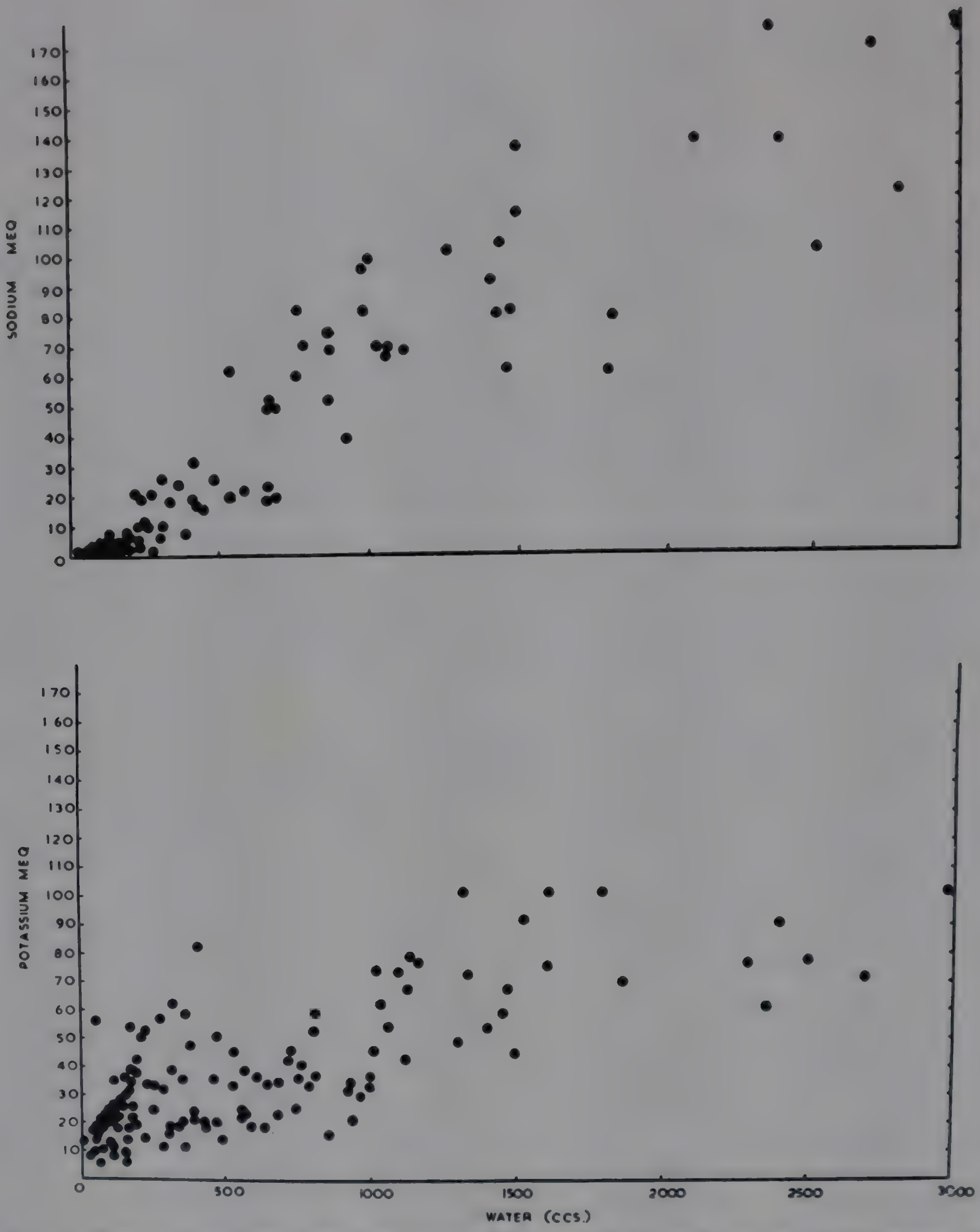


FIG. 1. Twenty-four hour fecal excretion of Na and K plotted against that of water in patients with steatorrhea.

posture during day and night or by renal disease. They also pointed out that the time of diuresis was influenced by the time of taking food and also that increasing the fluid intake increased the volume of the night urine rather than the daytime urine, though beyond a certain increase in intake, no further increase in nocturnal diuresis was effected and the daytime urine increased (Figure 2). One point of clinical interest emerging from these observations was that some patients with steatorrhea can give false positive results in Kepler's water test for Addison's disease. This point is especially important when it is remembered that many patients with steatorrhea are pigmented (a few may also have pigment in their mouths) and have low blood pressures, asthenia and often disturbed serum electrolytes. Wollaeger and Scribner focussed attention on the possible delayed absorption of water from the intestine. With the use of heavy water, Reitemeier, Higgins, Lee and Scholar have demonstrated that there is indeed a lower rate of absorption of water which rights itself as the patient improves (3). It is of interest that the rate was not speeded up by the administration of cortisone even though the patient's general condition approached normality with this therapy. French and Newsholme found a somewhat comparable delay in the absorption of Na^{24} (4).

Taylor has extended the initial observations of Wollaeger and Scribner (5–7). He agreed with their hypothesis of a delay in water absorption and pointed out the great delay in excreting water following the oral administration of a liter of water. He found a significant positive correlation between the degree of this delay and the degree of impairment of fat absorption. He did, however, find a

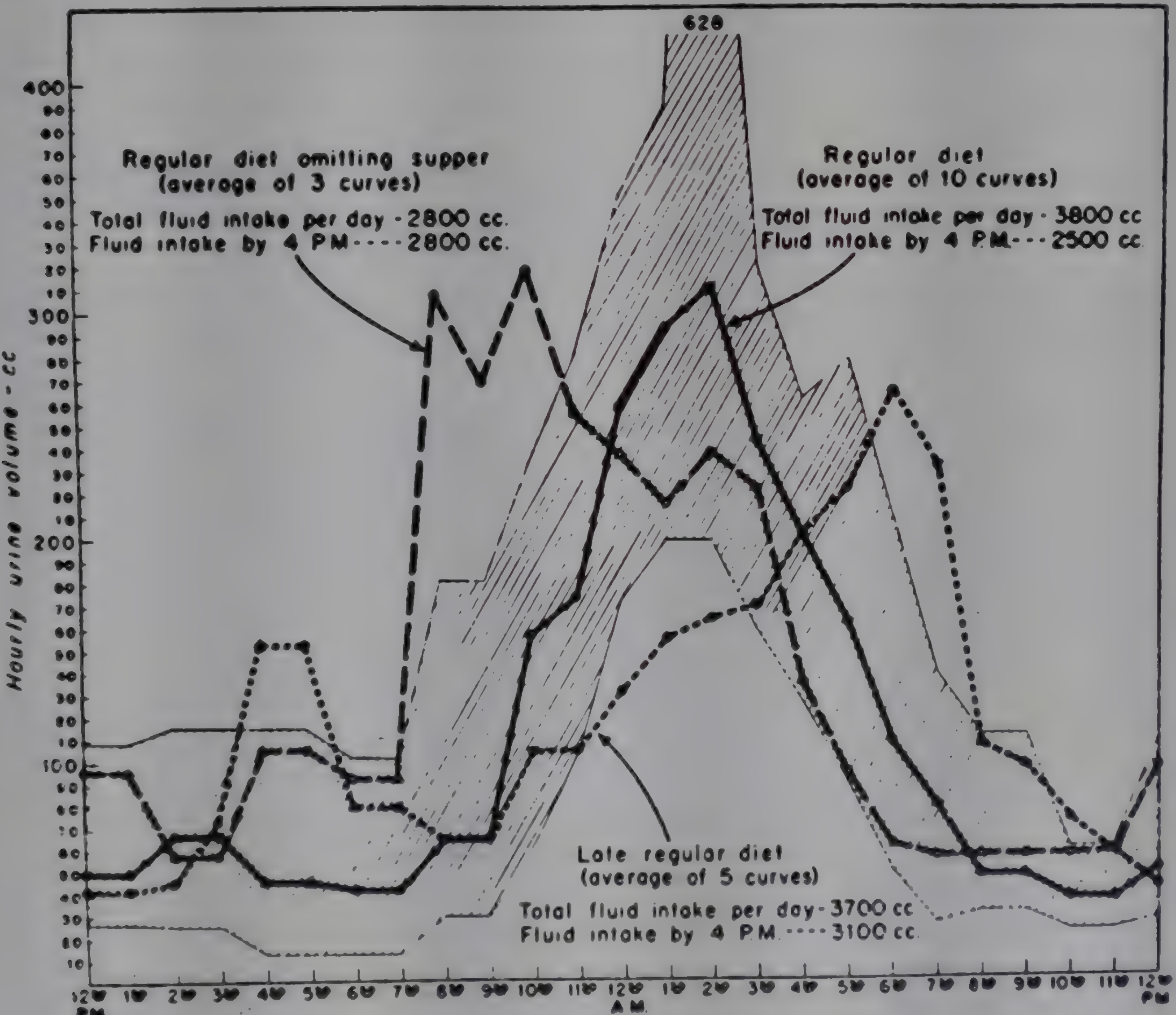


FIG. 2. Hourly volumes of urine of a patient with non-tropical sprue taking (1) the regular standard diet, (2) the same diet with meals delayed four hours and time of fluid ingestion kept approximately the same and (3) the same diet with omission of all food at 3:30 p.m. (Reprinted from Gastroenterology, 19: 224, 1951 (2)).

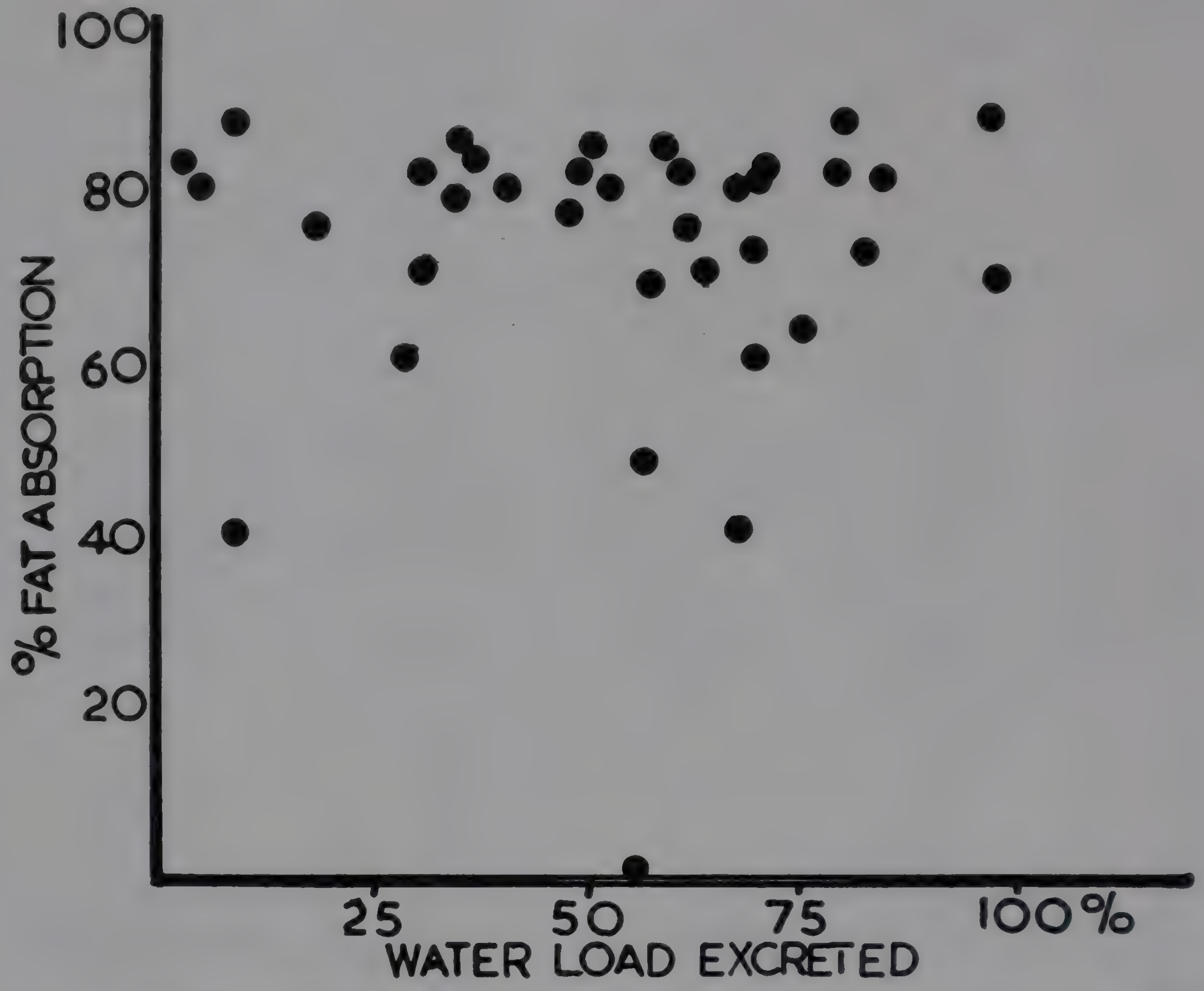


FIG. 3. Severity of steatorrhea, for convenience expressed as per cent absorption, plotted against a defect in water diuresis, expressed as the per cent excreted of the water load ingested.

similar delay in patients with untreated pernicious anemia which almost disappeared when treated, though not completely returning to normal. In pernicious anemia he believed that there was initially a delay in water absorption but a renal factor might also be implicated, preventing the complete return to normal. Observations in other conditions may provide a clue on the mechanism of the delayed diuresis in steatorrhea. In a series of 35 patients with steatorrhea, Flear and Cooke were unable to find any correlation between the degree of delayed diuresis and the defect in fat absorption (8) (Figure 3). Nor could any correlation be found between the diuretic response and the serum proteins or the hemoglobin. Little or no modification of the response was noted with hydrocortisone. The Na^{24} and K^{42} spaces were determined simultaneously in 11 patients, but again no correlation could be found between the delayed diuresis and the exchangeable masses of Na and K (Table I). Similar delays in diuresis were noted in patients with cirrhosis of the liver, congestive cardiac failure, ulcerative colitis and severe hypokalemia, while completely normal responses were obtained in two patients with severe hypoproteinuria. The similarity in response in these several conditions raises the question as to whether the apparent delay in water and sodium absorption is the complete explanation of this upset in water excretion. In one patient, the nocturnal diuresis continued unchanged during the administration of fluid continuously for seven days by a gastric drip, suggesting that there may well be some more fundamental defect causing this phenomenon. This suggestion was supported by observations on patients with regional ileitis with steatorrhea and apparently normal radiological patterns of the intestinal mucosa in the jejunum and upper half of the ileum. In none of these cases was the fecal excretion of water more than 400 ml. per day, but in all there was the same delay in diuresis and increased nocturnal excretion of water.

The possibility of renal changes playing some part cannot entirely be ruled out for the occurrence of tubular nephropathy has been reported by Ohler (9) and has been found in a number of our patients at post-mortem, though in none on whom the diuresis tests had been carried out (Figure 4). Whether the simple mechanical explanation of delayed absorption will prove the correct explanation for this upset in water excretion remains to be seen; but vitamin B_{12} deficiency, folic acid deficiency, chronic potassium depletion, liver dysfunction or even a functional disturbance of the brain stem may all play their part in bringing about this disturbance.

While the dangers of marked electrolyte depletion during any severe diarrhea is now well recognised, the development of severe deficits following a prolonged slight negative daily balance in patients with little or no diarrhea has not re-

TABLE I

Values for exchangeable potassium and sodium in patients with steatorrhea determined simultaneously with the water diuresis test

	Age	K_e	K_e/kg.	K_e/cm.	Na_e	Na_e/kg.	Na_e/cm.	3 hr. % Excretion‡
Male								
Mean normal*		3418	46.8	19.6	3029	41.6	17.3	
Coeff. var.		12.4	11.7	10.7	12.7	14.4	11.5	
Patients†	47	50.0	75.4	53.7	67.2	101.3	72.9	73
	58	58.9	72.3	61.7	86.6	106	91.3	30
	47	71.9	84.0	69.4	79.3	92.5	76.9	44
	33	57.2	83.6	60.3	94.8	139.2	100.6	62
	53	75.6	92.7	72.1	74.3	91.1	71.1	66
	25	70.4	105.1	75.5	63.3	95.2	68.2	94
	57	65.0	81.7	66.8	113.2	141.9	116.6	3
Female								
Mean normal*		2449	41.2	14.9	2328	40.2	13.8	
Coeff. var.		10.9	9.2	9.8	11.9	8.3	9.5	
Patients†	53	71.0	80.6	74.1	80.3	89.1	86.0	66
	49	58.0	91.5	65.8	119.6	183.8	139.2	58
	49	62.3	93.2	71.1	84.2	122.6	97.9	49
	26	66.1	91.0	69.1	93.2	124.8	100	60

* The values for normal have been computed from the literature and are expressed in absolute amounts (mEq.).

† The results in the 11 patients with steatorrhea are expressed as per cent of the mean normal values.

‡ The 3 hour excretion represents the per cent of the water load excreted during that time in the Kepler water test.

FOOD TECHNOLOGICAL RESEARCH INST
3923
LIBRARY

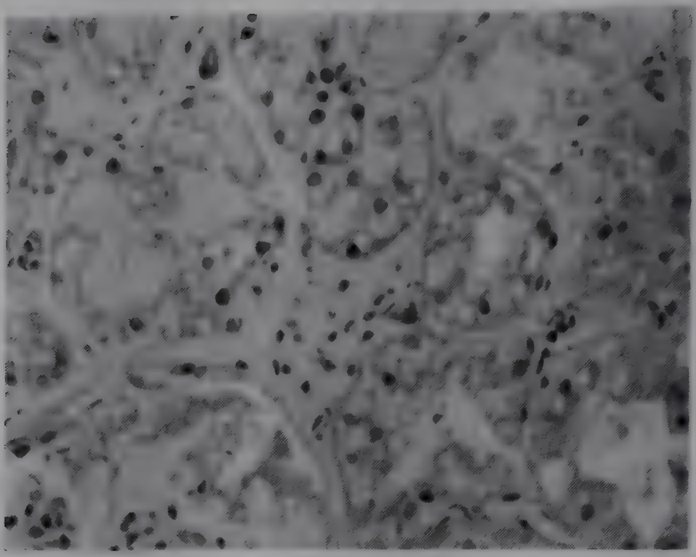


FIG. 4. A photomicrograph of kidney showing tubular nephropathy associated with potassium deficiency in a 53-year old man who died with idiopathic steatorrhea. This patient had become depleted of electrolytes on a number of occasions during the 6 years he was under observation and, although no controlled observations had been made on water excretion, he had marked nocturnal diuresis during his periods of ill health.

ceived as much attention as it deserves. In order to give quantitive backing to this belief, Blainey, Cooke, Quinton and Scott studied the available stores of potassium with isotopes in 12 patients with idiopathic steatorrhea (10). They found that the values for the males and females were only 63 and 58 per cent of the mean normal values computed from values in the literature. These initial observations were considerably extended by Flear, Quinton, Cawley and Cooke on a further 23 patients (11). A number of different conditions were studied, though the majority of patients were suffering from non-tropical sprue; none had any evidence of marked dehydration. In 21 of the 23 patients studied by this technique the exchangeable values for potassium were significantly lowered, the other two being 81 and 82 per cent of the mean normal levels and in good health at the time of the observations. The results in the other 21 patients, however, might have meant only that the patients had all lost weight, for when the results were standardized to a unit of body weight, 16 were not significantly different from normal though only five had values equal to or greater than the mean normal. The remaining five patients had evidence of intracellular depletion of potassium. By analyzing the data with exchangeable potassium referred to a unit of body height, evidence could be obtained that the lower total exchangeable potassium in 16 of the 23 patients was due to intracellular depletion of potassium and loss of lean tissue combined. The exchangeable K (K_e) for the 34 observations in 23 patients was 58.7 per cent of the mean normal (range 15.6–82.0), expressed as mEq. per kg.—77.8 per cent (range 27.3–105.7), expressed as mEq. per cm.—63.7 per cent (range 16–86.7). A similar analytical approach to the data of Blainey et al. suggested that, of the 12 patients, in 9 the lowered K_e was due to loss of intracellular potassium and lean tissue and in the remaining three, there was loss of intracellular potassium and body fat with or without lean tissue loss in addition.

In 20 of these patients, the exchangeable stores of sodium were estimated

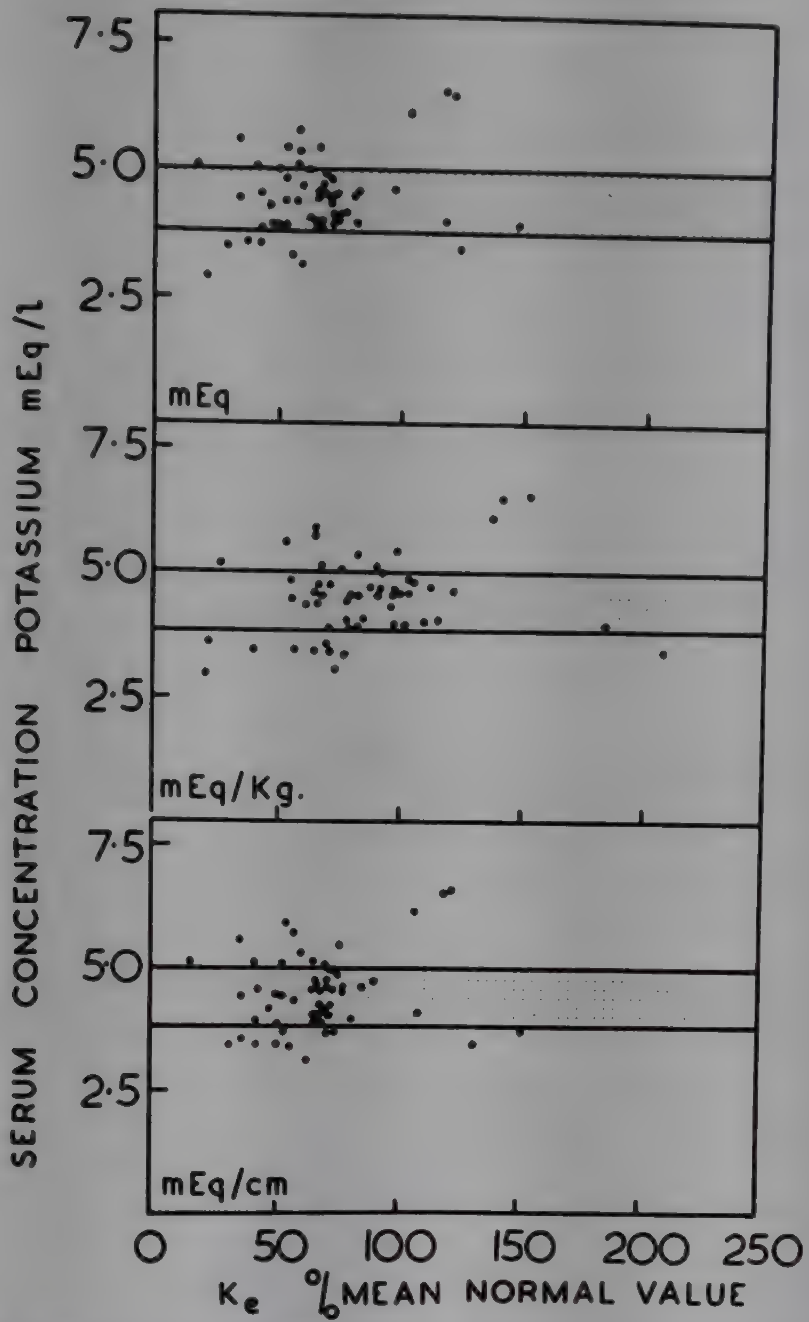


FIG. 5. Fifty-six observations on 38 patients with steatorrhea, showing absence of relationship between serum K and K_e (expressed as percentage of mean normal values.) Shaded areas represent the normal range (80 per cent confidence, Wootton, I. D. P., King, E. J., Lancet, *i.e.*, 470, 1953.)

simultaneously with those of potassium. There was little evidence of any significant deviation from the mean normal in these patients and in 12 the results fell within normal ranges. For the 20 patients, exchangeable (Na_e) was 103.3 per cent of mean normal (range 78.0–139.4), expressed as mEq./kg.—110.7 per cent (range 72.6–141.9), as mEq./cm.—92.5 per cent (range 68.2–139.2). Since none of these patients was suffering from severe diarrhea or had evidence of gross dehydration at the time of study, these results are not surprising.

As has been pointed out by Moore et al. serum levels of potassium are not a reliable guide to the stores of exchangeable potassium (12). In Figure 5, the findings in a series of 38 patients are depicted. It can readily be seen that the serum values within normal ranges have little significance. It is important to realize, therefore, that many patients with steatorrhea have deficient stores of

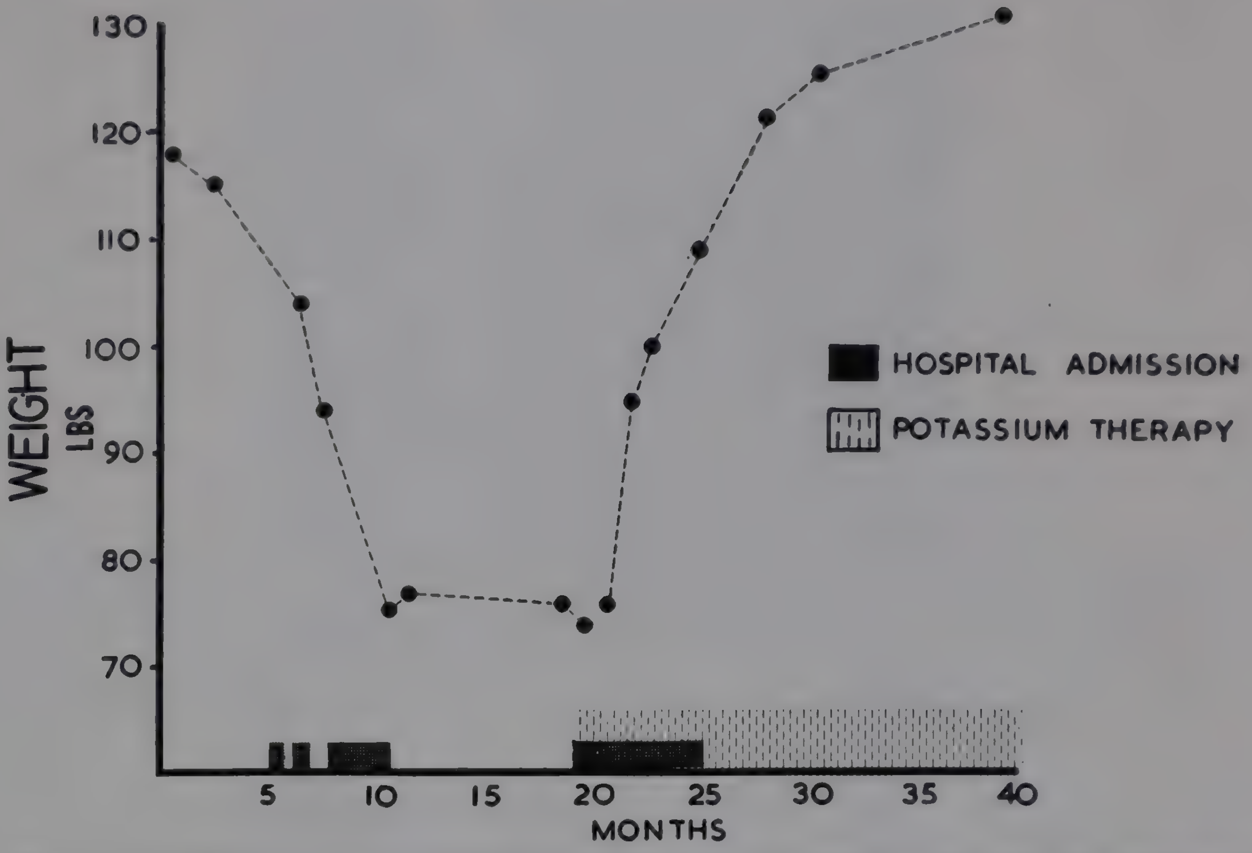


Fig. 6. The effect on weight of addition of potassium therapy in a 56-year old woman with regional ileitis and a bipassed loop.

available potassium and that in some this deficiency will be of severe degree. In view of this, it is still more important to recognize the symptoms which may be produced, in some part at least, by potassium deficiency.

Weight loss. Weight loss is one of the commonest symptoms in the malabsorption syndrome. In a series of 100 patients with non-tropical sprue Cooke, Peeney and Hawkins found that the average weight loss at the time the patients were first seen was 28 pounds (13). There are of course many factors bringing this about, but, unless there are adequate stores of potassium, the patient will find it difficult to regain his normal weight. In a few patients, it can be demonstrated that extra supplements of potassium are all that is necessary to allow return to normal weight. A particularly striking, though probably exceptional, example is depicted in Figure 6.

This woman was first seen in 1945, aged 52, on account of diarrhea and progressive loss of weight during the previous five years. In 1939 an ileo-colectomy without exclusion had been performed for an obstructive lesion in the right iliac fossa, thought to be regional ileitis. On admission, she weighed 73 lb. Her blood count was 1.9 million red cells and hemoglobin 8.0 gm., MCV 150 cu.μ. She was excreting over 40 gm. of fat daily. Treatment with a crude liver extract caused her blood to revert slowly to normal values. At the end of 12 months the red cell count was 4.92 million, hemoglobin 14.8 gm., MCV 84 cu.μ. Her weight increased to 140 lb. Despite persistence with regular liver therapy and admission to the hospital on two occasions her weight gradually fell over the next four years to 73 lb. The addition of folic acid had restored her blood count to normal while calciferol, nicotinic acid and riboflavine controlled her cramps and glossitis. In 1950 she was admitted mentally confused and greatly wasted. Her serum potassium was found to be 3.0 mEq. per liter. Dehydration was corrected; therapy with folic acid, liver extract and B vitamins was continued and intensive potassium therapy initiated. Her weight increased as depicted in

Figure 6. Her blood count was maintained at normal levels; her loose stools continued 5–6 times daily and she was able to run her home. In 1955, following a severe attack of diarrhea, she had a severe prolapse of her rectum. X-ray investigation confirmed the provisional diagnosis that a large portion of the small intestine had been bypassed. An operation was, therefore, performed which revealed an anastomosis between the jejunum, one foot below the duodeno-jejunal flexure, and the transverse colon and normal continuity was restored. The remainder of the small intestine was normal except for a number of scars involving the wall of the mid-portion of the ileum. Following operation, her diarrhea ceased, she passed normal colored, formed motions 1–2 a day. Her fat excretion, which was 10–15 gm. per day prior to operation, fell to 6 gm. per day 10 days after operation. No further therapy has been given. Her weight is now constant 18 months after operation at 142 lb. and her blood count normal in all respects.

Intestinal distension and ileus. Streeten and his colleagues have demonstrated the importance of the normal electrolyte content of the intestinal cell for the maintenance of the normal tone of the intestinal muscle (14). With increasing depletion of intracellular potassium, ileus eventually becomes manifest. The possible importance of this work in the steatorrhea syndrome is self evident. It may well provide the explanation for the increase of the intestinal lumen, a characteristic finding on radiological examination of the small intestine in idiopathic steatorrhea. In minor degrees of depletion, abdominal distension is common. Such symptoms have usually been attributed to intestinal fermentation with excessive gas formation, but the relief obtained with potassium therapy suggests that potassium deficiency is probably a primary cause.

More dramatic manifestations are those of volvulus and intestinal obstruction. Adlersberg and Glazer have drawn attention to this group of patients and the importance of early recognition to prevent actual gangrene of the gut (15). In many patients with steatorrhea, the colon appears to be excessively long, thus it is not surprising to meet, in such patients during periods of abdominal distension, attacks of abdominal pain, often relieved by the adoption of the knee-elbow position. The distension of any hollow tube, e.g. a bicycle tube, within a semi-rigid container is obviously liable to cause kinking and obstruction to the free passage of the contents of that tube. Clinically, such kinking may simulate acute intestinal obstruction sufficiently closely to mislead the most experienced. Adlersberg has described the volvulus that may occur. Recognised early, vigorous restoration of fluids and electrolytes will relieve the condition, though should the attack be of such duration as to raise doubt on the possible viability of the bowel, laparotomy may be necessary also.

Another confusing picture that may appear independantly of the attacks of abdominal pain is recurrent vomiting which has been the presenting symptom in a few patients, suggesting either pyloric stenosis or gastric neoplasm. Such vomiting is due to partial volvulus of the stomach associated with the general intestinal atony, the dilated colon displacing the stomach and so bringing about the volvulus.

Neuropathy and mental disorder. Neuropathy is not uncommonly encountered in the malabsorption syndrome, showing itself in a variety of ways—peripheral neuritis, cord degeneration and, occasionally, cerebral or cerebellar degeneration.

In a study of 26 such cases, no evidence of a primary potassium deficiency could be found, though in view of Biermond and Polkadaniels' observations in periodic paralysis, chronic potassium deficiency might play some part in the initiation of organic nervous disease (16). Severe hypokalemia will on occasions be associated with a peripheral neuritis which rapidly clears up with the relief of the hypokalemia. Similarly, severe psychoses occasionally occur and, with the underlying cause not being recognized, may result in the patient being committed to a mental hospital (17).

Tetany. Tetany has long been recognised as one of the features of the severe sprue syndrome. It is, however, rare to find a patient with troublesome recurrent tetany who does not also have fairly severe depletion of potassium. The recognition of this association has enabled us successfully to relieve patients who had long resisted conventional therapy with extra calcium and vitamin D and to restore normal levels of calcium in the serum. This was strikingly demonstrated in one patient with such symptoms in whom complete relief was obtained with intensive potassium therapy and rehydration but without any added calcium or vitamin therapy. The demonstration of increased urinary excretion of phosphate during hypokalemia by Mahler and Stanbury adds another factor to be considered (18). However, much remains to be discovered about the complicated mechanisms of calcium metabolism and its relationship to electrolyte depletion.

Asthenia and lassitude. Finally, asthenia and lassitude are the commonest symptoms in steatorrhea. Although non-specific they are both, nevertheless, symptoms of potassium depletion. Accordingly, it has become the practice of this clinic to give as routine therapy, potassium supplements, such as KCl 1–2 gm. t.i.d., whenever the patient is not well and to all patients with steatorrhea periodically.

SUMMARY

To conclude, there is evidence that patients with steatorrhea tend to get depleted of potassium. There is no evidence that the upsets in water excretion and electrolyte metabolism are other than secondary manifestations. However, in view of the widespread importance of potassium in a large variety of processes in the body, it would appear wise to maintain the potassium stores at normal levels.

REFERENCES

1. Cooke, W. T., Thomas, G., Mangall, D., and Cross, H.: Observations on the Faecal Excretion of Total Solids, Nitrogen, Sodium, Potassium, Water and Fat in the Steatorrhoea Syndrome. Clin. Sci., 12: 223, 1953.
2. Wollaeger, E. E., and Scribner, B. H.: Delayed Secretion of Water with Regular Nocturnal Diuresis in Patients with Nontropical Sprue (Idiopathic Steatorrhea). Gastroenterology, 19: 224, 1951.
3. Reitemeir, R. J., Higgins, J. A., Lee, E. R., and Scholar, J. F.: The Absorption of Water and Sodium from the Small Bowel of Patients with Non-tropical Sprue. J. Clin. Invest., 35: 730, 1956.
4. Newsholme, G. A., and French, J. M.: Absorption of 24 NaCl from the Small Intestine in the Sprue Syndrome. Clin. Sci., 13: 607, 1954.

5. Taylor, W. H.: Water Diuresis in Idiopathic Steatorrhoea. Clin. Sci., 13: 239, 1954.
6. Taylor, W. H.: Water Diuresis in Pernicious Anaemia. Clin. Sci., 14: 497, 1954.
7. Taylor, W. H.: Water Absorption in Idiopathic Steatorrhoea. Clin. Sci., 14: 725, 1955.
8. Flear, C. T. G., and Cooke, W. T.: Unpublished Observations, 1956.
9. Oehler, V.: Pathological and Anatomical Studies of Seven Cases of Idiopathic and Symptomatic Sprue. Gastroenterologia (Basel), 79: 257, 1953.
10. Blainey, J. D., Cooke, W. T., Quinton, A., and Scott, K. W.: The Measurement of Total Exchangeable Potassium in Man, with Particular Reference to Patients with Steatorrhoea. Clin. Sci., 13: 165, 1954.
11. Flear, C. T. G., Quinton, A., Cawley, R., and Cooke, W. T.: Clin. Sci., (In Press).
12. Moore, F. D., Edelman, I. S., Olney, J. M., James, A. H., Brooks, L., and Wilson, G. M.: Body Sodium and Potassium, 3. Interrelated Trends in Alimentary, Renal and Cardiovascular Disease: Lack of Correlation between Body Stores and Plasma Concentration. Metab., 3: 334, 1954.
13. Cooke, W. T., Peeney, A. L., and Hawkins, C. F.: Symptoms, Signs and Diagnostic Features of Idiopathic Steatorrhoea. Quart. J. Med., 22: 59, 1953.
14. Streeten, D. H. P., and Vaughan Williams, E. M.: Loss of Cellular Potassium as a Cause of Intestinal Paralysis in Dogs. J. Physiol., London, 118: 149, 1952.
15. Glazer, I., and Adlersberg, D.: Volvulus of the Colon: a Complication of Sprue. Gastroenterology, 24: 159, 1953.
16. Biermond, A., and Polkadaniels, A.: Familial Periodic Paralysis and Its Transition into Spinal Muscular Atrophy. Brain, 57: 91, 1934.
17. Cooke, W. T.: Nutritional and Metabolic Factors in the Aetiology and Treatment of Regional Ileitis. Ann. Roy. College of Surgeons, England, 17: 137, 1955.
18. Mahler, R. F., and Stanbury, S. W.: Potassium-losing Renal Disease; Renal and Metabolic Observations on a Patient Sustaining Renal Waste of Potassium. Quart. J. Med., 25: 21, 1956.

INTESTINAL UPTAKE OF VITAMIN B_{12} IN THE MALABSORPTION SYNDROME

SANFORD OXENHORN,* M.D.

SOLOMON ESTREN, M.D.

AND

DAVID ADLERSBERG, M.D.

New York, N. Y.

It has been known for some time that liver extract and more recently vitamin B_{12} are useful agents in the treatment of some patients with the malabsorption syndrome (1–4). Bioassay methods have revealed a low serum B_{12} level in many of these patients (5). It has therefore been suggested that a defect in vitamin B_{12} absorption is present in the malabsorption syndrome. In addition, actual malabsorption of vitamin B_{12} has been demonstrated in patients with sprue (6–14).

VITAMIN B_{12}: CHEMISTRY AND QUANTITATIVE ANALYTICAL METHODS

In 1948 the crystallization of vitamin B_{12} from liver was achieved (15). Biosynthesis was accomplished shortly thereafter utilizing the micro-organism *Streptomyces griseus* (16). This organism was employed in the production of radioactive vitamin B_{12} by adding Co^{60} to the culture medium (17).

Using x-ray crystallography techniques, Hodgkin (18, 19) has recently determined the complete structural formula of vitamin B_{12} (Fig. 1). The empirical formula is $C_{63}H_{88}O_{14}N_{14}PCo$; the molecular weight is approximately 1350. The molecule resembles a porphyrin with a single central cobalt atom. Its shape is spherical with all of the chemically reactive groups located on the surface.

Among the available methods for measuring vitamin B_{12} content are chemical techniques employing colorimetry, spectrophotometry or isotope dilution. Unfortunately, these methods fail to detect the low levels present in animal body fluids. They also fail to differentiate B_{12}-like substances from vitamin B_{12}. Bioassay techniques which measure the growth response of B_{12}-dependent bacteria or protozoa are far more sensitive although not entirely specific.

ABSORPTION, TRANSPORT AND STORAGE OF VITAMIN B_{12}

The main food source of vitamin B_{12} is animal protein, particularly liver. It is present in certain forms of plant life as well. Smith believes that B_{12} is derived from microbial synthesis in both of these sources (20).

From the Departments of Hematology and Medicine, The Mount Sinai Hospital, New York, N. Y.

* Present address: Department of Medicine, Maimonides Hospital, Brooklyn, New York.

These studies were supported in part by the Albert A. List, Frederick Mochlin, and Anna Ruth Lowenberg Funds; and by grants from Merck and Company, Rahway, New Jersey.

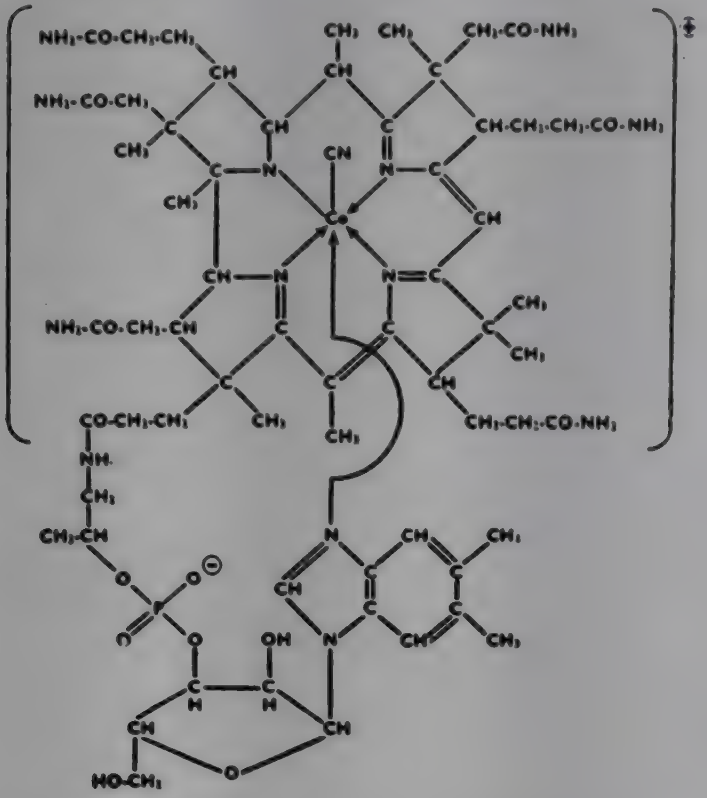


FIG. 1. Structural formula of vitamin B_{12} as depicted by Hodgkin et al. (18).

When food containing vitamin B_{12} enters the stomach it encounters an as yet unidentified substance liberated by the fundic cells in the human being, termed by Castle intrinsic factor (IF). Although the specific mode of action of IF remains to be clarified, it is safe to assume that it is necessary for the absorption of dietary vitamin B_{12}. It is doubtful whether it plays a role in the absorption of the huge oral doses used in some studies (21,22). By the use of tagged vitamin B_{12} in patients with pernicious anemia, it has been shown that a stoichiometric relationship existed between the quantity of IF administered and the amount of B_{12} absorbed in the dosage range of less than 1.0 μg. of the vitamin (23). This phenomenon suggests a physico-chemical reaction. However, the rather limited ability of the small intestine to absorb vitamin B_{12} beyond 1 μg. amounts, regardless of the presence of abundant IF, has led Glass to postulate a "partial mucosal block" mechanism resembling the apoferritin system of iron absorption (24) (Fig. 2). In addition, there is a characteristic absorption delay after the ingestion of vitamin B_{12} with peak plasma levels appearing 8 to 12 hours postprandially (25) (Fig. 3).

Approximately 80 to 90 per cent of the circulating vitamin B_{12} is bound to plasma protein. Studies employing both paper electrophoresis of serum and bioassay have located the bound B_{12} with the alpha globulins (26). Intravenous injections of radio-active vitamin B_{12} have demonstrated a rapid loss of isotope from the plasma with the accumulation of activity over the liver in 2 to 4 minutes (27). At the end of 6 to 10 days the major portion of absorbed vitamin B_{12} is stored in the liver (28).

Only a small quantity of vitamin B_{12} is eliminated into the urine. On the other hand, feces contain considerable amounts of B_{12}, derived both from the unabsorbed vitamin in food and from a portion synthesized by the bacterial flora of

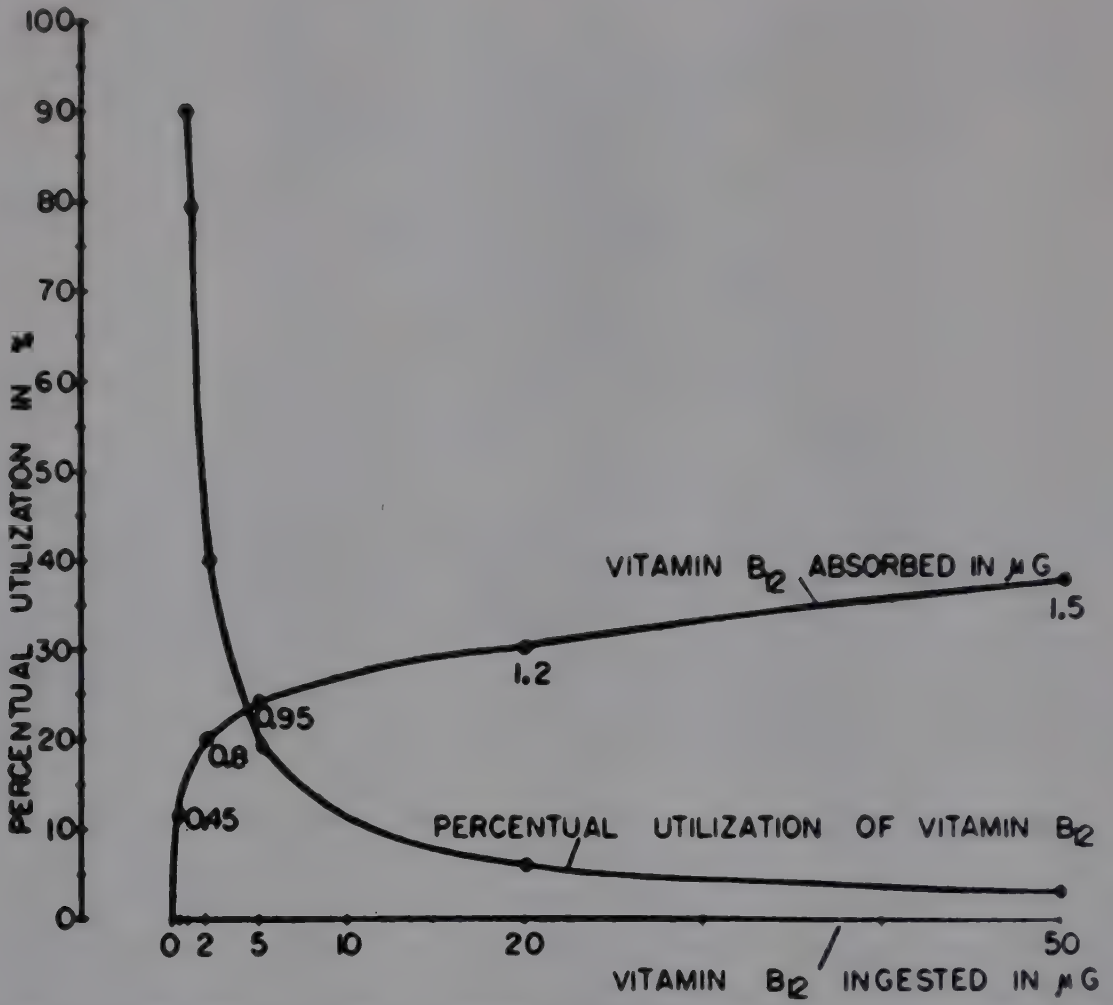


FIG. 2. The intestinal block to vitamin B_{12} in normal humans as shown by the addition of increasing oral doses (0.5–50.0 µg.) of labeled vitamin B_{12}. Using the liver uptake method, Glass demonstrates the sharp fall in the percentage absorbed when more than 1.0 µg. B_{12} is administered (36).

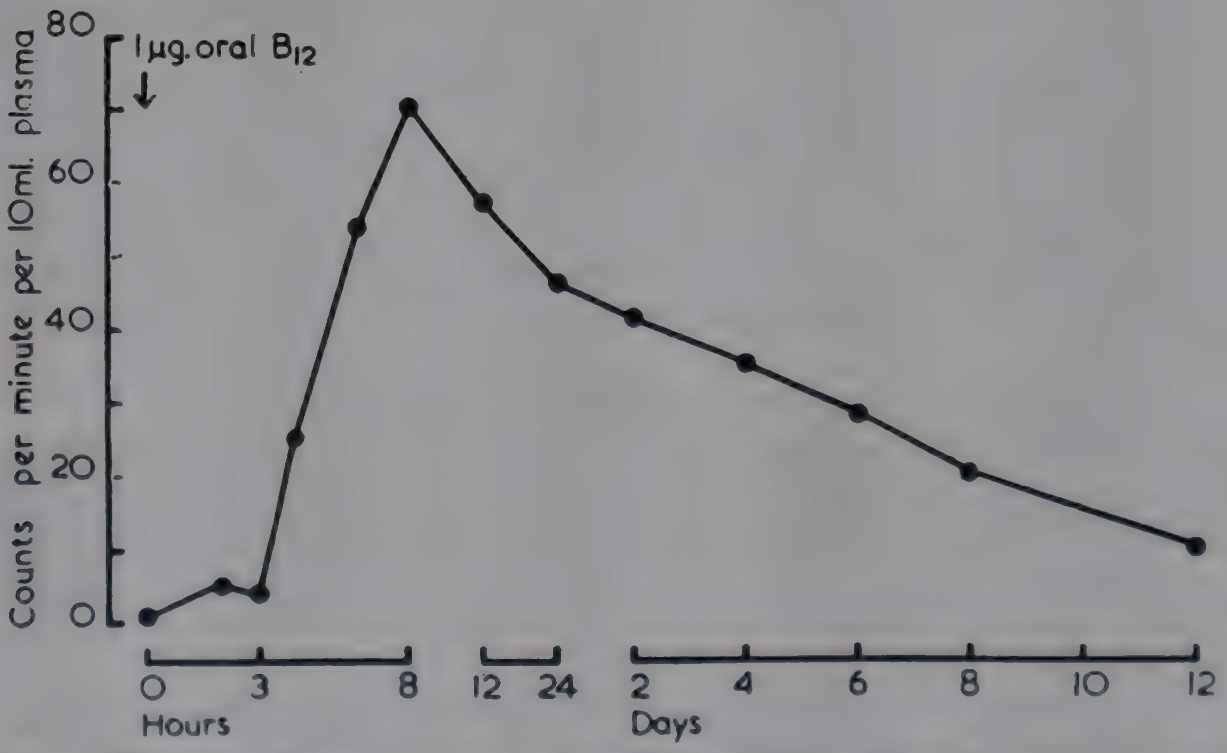


FIG. 3. Plasma radioactivity after an oral dose of 1.0 µg. of radioactive vitamin B_{12} given to a control subject (25).

TABLE I

Vitamin B_{12} Deficiency States in Relation to Site of Disturbance

Group	Site of Disturbance	Mechanism of Deficiency	Clinical State
A	Food	Deficient diet	Nutritional macrocytic anemia
B	Stomach	Deficient intrinsic factor	1. Pernicious anemia 2. Total gastrectomy 3. Gastric neoplastic infiltration
C	Small Intestine	Defective absorption	1. Idiopathic sprue 2. Sprue syndrome secondary to Whipple's disease, lymphoma, intestinal resection, strictures, diverticula or fistulae 3. Blind loop syndrome 4. *D. Latum* infestation
D	Miscellaneous	Metabolic defects	1. Liver disease? 2. Anti-vitamin?

the colon. This synthesized B_{12} is probably unavailable to the host since B_{12} absorption occurs almost exclusively in the small intestine. Table I shows the diseases of vitamin B_{12} deficiency in relation to the supposed site of disturbance.

METHODS OF STUDYING THE INTESTINAL ABSORPTION OF VITAMIN B_{12}

1. *Hematologic response.* Castle's original method for the detection of the anti-pernicious anemia factor was based on the clinical and hematologic response of a patient with pernicious anemia in relapse following the oral administration of the test material. The same method may be applied to the absorption of vitamin B_{12}, but in addition to the difficulty in obtaining such patients, it has limited value as a quantitative technique. Further, the unpredictability of absorption in any given patient with pernicious anemia has recently been demonstrated by the observation that in certain patients in relapse as little as 5 μg. of vitamin B_{12}, administered orally without IF, resulted in a clinical and hematologic remission (29).

2. *Bioassay techniques.* Serum vitamin B_{12} levels are abnormally low in the megaloblastic anemias (5). Attempts to devise a test of vitamin B_{12} absorption based on serum bioassay methods have failed because when physiologic amounts of the vitamin are administered orally (1.0 μg. or less) no increase in serum vitamin B_{12} content is demonstrable even in normal subjects. It is only when the oral dose of vitamin B_{12} exceeds 500 μg. that the bioassay method reveals an increase in serum vitamin B_{12} (21). Since patients with pernicious anemia absorb B_{12} at these high dosage levels as well as control subjects, it would appear that under these circumstances absorption is independent of IF. Therefore, this method is useful in the detection of states of vitamin B_{12} depletion, but not as an absorptive test.

TABLE II

Radioactive isotope methods to study intestinal absorption of B_{12}

Test Material or Site	Duration of Test	What Test Measures	Author of Test
Stool	7 days	Unabsorbed isotope	Heinle, Welch, et al., 1952 (30)
Urine	24 hours	Absorbed isotope "flushed" into urine	Schilling, 1953 (31)
Liver	6–10 days*	Absorbed isotope stored in liver	Glass et al., 1954 (32)
Plasma	8–12 hours	Absorbed isotope in plasma	Booth and Mollin, 1956 (25)

* Recently modified to a 48 hour test.

3. *Radio-active vitamin B_{12}.* Oral doses of B_{12} labeled with Co^{60}, Co^{58} or Co^{56} have been the most useful tools for studying intestinal absorption (30–33, 25). The methods available at present are shown in Table II. The stool method is based on the assumption that whatever radio-activity has not appeared in the feces, during a standard collection period, has been absorbed. Although it is an indirect technique, it probably permits the most nearly quantitative estimation of vitamin B_{12} absorption of any of the methods employed. The liver and plasma methods measure in a direct way a portion of the absorbed isotope. The former depends, among other factors, on the ability of the liver to store B_{12}. The urinary excretion method utilizes a 1000 μg. intramuscular "flushing dose" of non-radio-active B_{12} to produce a diuresis of this vitamin. With the test performed in this manner, the 24 hour urine contains approximately one-third of the absorbed isotope-tagged B_{12} (34).

METHODS AND MATERIALS

Clinical material. This report is based on a study of the following groups of persons:

Group 1. Control subjects: 12 females, 11 males, with no demonstrable disease of the gastrointestinal tract, hematopoietic system, liver or kidney.

Group 2. Pernicious anemia: 8 females, 7 males in whom the diagnosis was established on the basis of hematologic studies, gastric analysis and a typical response to vitamin B_{12} therapy. There was no evidence of intestinal disease in this group.

Group 3. Idiopathic sprue: 16 females, 9 males, selected on the basis of a typical clinical picture with characteristic laboratory and roentgenologic findings of the malabsorption syndrome.

Group 4. Intestinal resections: 2 patients with a large portion of small intestine surgically removed in the treatment of jejuno-ileitis, and a third patient who had 90 per cent of the small bowel resected following occlusion of the superior mesenteric artery.

Laboratory methods. The following are the studies performed and the methods used:

1. Hematologic studies of bone marrow and peripheral blood.
2. Roentgen studies of the stomach, small intestine and colon.
3. Studies of intestinal absorption: oral glucose tolerance test; vitamin A tolerance test; serum carotene level; fecal fat partition; prothrombin time; serum Na, K, Cl, CO_2, Ca and P; serum iron; serum proteins and serum vitamin B_{12} level.
4. Schilling test method, modified as follows:

a. All patients were studied in the early morning following a period of 12 to 16 hours of

TABLE III

Comparison of Schilling's original method and authors' modification of urinary excretion test

	Schilling's Method	Our Modification
Oral dose in μg. of labelled B_{12}	2.0	0.4–0.5
Interval between oral and "flushing" dose in hours	2	0
Controls:		
% of oral dose excreted in 24 hours	7–21	9–36
Pernicious Anemia:		
% of oral dose excreted in 24 hours	0–2.3	0–1.2
Malabsorption Syndrome:		
% of oral dose excreted in 24 hours	—	0–19.0

fasting. No vitamin preparations were permitted during the 48 hour period prior to and on the day of the test.

b. 0.4 to 0.5 μg. of radio-active vitamin B_{12} tagged with Co^{58} or Co^{60} was administered orally in 75 to 100 ml. of water.

c. 1000 μg. of non-radio-active B_{12} was injected intramuscularly immediately thereafter.

d. In most of the persons under study, the test was repeated after one week or more, adding a 30 mg. dose of intrinsic factor concentrate along with the oral vitamin B_{12}. This IF material was of proved potency from a single batch of material* employed in each case.

e. Patient was allowed only coffee and toast one hour after the test dose and a regular diet three hours after test dose and for the remainder of the day.

f. A 24 hour urine collection was obtained.

g. A 500 ml. aliquot was then added to a bottle of fixed dimensions and placed over a thallium-activated NaI crystal scintillation counter. Then 25,600 counts were obtained of the unknown urine sample and compared with a water blank as well as with a radioactive standard solution obtained from the same isotope lot. When previous isotope administration had occurred, a urine blank was used. Results were expressed in percentage of administered dose excreted in the 24 hour urine.

It is evident that Schilling's original technique was modified in respect to the isotope dose and time interval between that dose and the administration of the non-radio-active vitamin B_{12}. The details of this modification and comparative results with Schilling's method are shown in Table III.

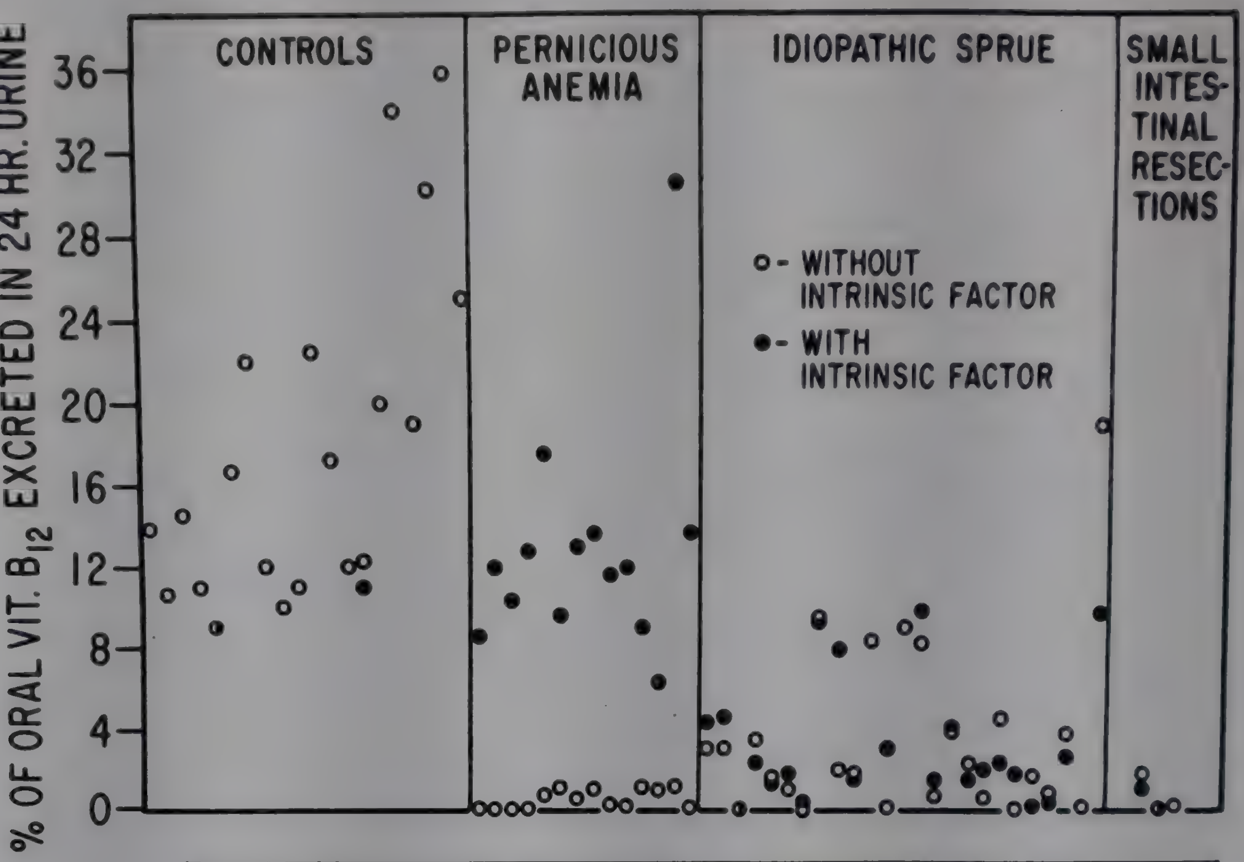
The use of a smaller oral dose (0.4 to 0.5 μg.) of B_{12}, with which dose the percentage absorption is greater than with the 2.0 μg. dose, was made possible by the recent availability of radio-cobalt vitamin B_{12} of high specific activity.

RESULTS

The urinary excretion of labeled B_{12} is shown for all four patient groups in Figure 4. The 20 control subjects had an average of 17.9 per cent of the oral dose in their 24 hour urine with a range of 9.0 to 35.8 per cent. All 14 patients with pernicious anemia had excretions below 1.2 per cent. However, upon the addition of intrinsic factor, 13 excreted in the normal range with only one patient slightly below this range (6.3 per cent). In the group with idiopathic sprue, the average excretion was 3.6 per cent. Of these, 20 patients had marked impairment of B_{12} urinary excretion, four had low normal results and the excretion of one

---

* Generously supplied by Abbott Co. Lot E-5872.



	CONTROLS	PERNICIOUS ANEMIA		IDIOPATHIC SPRUE		SMALL INTESTINAL RESECTIONS	
	NO I.F. (○)	NO I.F. (○)	I.F. (●)	NO I.F. (○)	I.F. (●)	NO I.F. (○)	I.F. (●)
AVERAGE	17.9	0.5	12.9	3.6	3.3	0.63	0.6
RANGE	9-36	0-1.2	6.3-30.5	0-19	0-10	0-1.8	0-1.1

FIG. 4. Scattergraph of urinary excretion tests in control subjects as well as in patients with pernicious anemia, idiopathic sprue and extensive intestinal resections. The open circles represent the excretion of labelled vitamin B_{12} given orally. The closed circles represent the excretion of labelled vitamin B_{12} given orally *with* intrinsic factor. Each test on the same patient is placed in vertical alignment.

was in the normal range. The three patients with massive resections of the small intestine had virtually no detectable isotope in their urine. It is clear (Fig. 4) that intrinsic factor fails to improve the defective radio-B_{12} excretion in either idiopathic or secondary sprue.

Figure 4, therefore, demonstrates that the impairment in B_{12} absorption, as measured by the urinary excretion test, is less marked in most of the patients with the malabsorption syndrome than in the pernicious anemia group. Further, the characteristic improvement in vitamin B_{12} absorption achieved when a source of intrinsic factor is added to the latter group is lacking in the sprue patients studied.

DISCUSSION

In order to compare the results of this communication with those of previous reports it is necessary to contrast both the urinary excretion test method and the selection of patients for each clinical group. The use of a 0.4 to 0.5 μg. oral dose of radio-cobalt vitamin B_{12} has served to increase the average 24 hour isotope excretion of normal subjects (expressed as per cent) as compared with the 2.0 μg. dose. Therefore, the smaller dose has widened the gap between the malabsorber and the normal-absorber. As stated above, Callendar and Evans (34) have shown that approximately one-third of the vitamin B_{12} absorbed appears in the urine following a "flushing" dose. Therefore, the Schilling test may be used as a semi-quantitative index of vitamin B_{12} absorption.

Regarding patient selection, there can be little disagreement concerning a precise diagnosis of pernicious anemia when all clinical and laboratory criteria are properly employed. On the other hand, the term "malabsorption syndrome" is applied to a variety of disease states. In this report we have included only a single type of secondary sprue, namely, that resulting from the surgical removal of large portions of the small intestine. All of the remaining patients fell into the category of idiopathic sprue; i.e., they presented at some time in their course with weight loss, diarrhea and steatorrhea—without evidence of a gross anatomic lesion in their small intestine. The symptomotology of these patients is discussed in more detail elsewhere in this symposium. In each patient there was laboratory evidence of an absorption defect for one or more nutrients besides vitamin B_{12}. Most of this group had the roentgenologic changes of the small intestine of the type seen in idiopathic sprue (35).

There is agreement among most authors that vitamin B_{12} absorption is deficient in some patients with the sprue syndrome. However, since patients with different types of steatorrhea are included in the same statistical group by certain authors, the incidence of B_{12} malabsorption varies among these reports. Thus in one group of 13 patients with steatorrhea, seven were found to have defective B_{12} absorption, but among the malabsorbers there were two patients with diffuse diverticulosis (13). In another study of seven patients with sprue, four showed low levels of B_{12} excretion without IF administration (9). Other smaller groups of patients have been reported which showed this defect in B_{12} absorption as measured by the stool, urine or liver methods (7, 10, 11).

While most authors report no improvement in the vitamin B_{12} absorption following the addition of IF in patients with sprue, it should be mentioned that Callender and Evans demonstrated an apparent enhancement of absorption by adding very large doses of IF (up to 2000 mg.) (13). However, in the same patients ordinary doses of IF (25 to 50 mg.), which were sufficient to correct the defective absorption of B_{12} in pernicious anemia, failed to exert this effect.

The detection of a defect in vitamin B_{12} absorption in a given case reduces the diagnostic possibilities to a limited group of gastrointestinal disorders. The disturbances related to stomach malfunction (Group B of Table I: pernicious anemia, gastric carcinoma and gastrectomy) are all corrected by the addition of IF, whereas the intestinal disturbances (Group C) are not improved by IF. The so-called "intestinal stasis" disorders (diverticulosis, strictures, blind loop syndrome) may show a return to normal B_{12} absorption following antibiotic therapy, (14) thus adding another tool in the differentiation of vitamin B_{12} malabsorption syndromes (Table IV).

TABLE IV

Differentiation of B_{12} malabsorption states

	B_{12} alone	B_{12} + IF	B_{12} + antibiotics
Pernicious anemia....	poor absorption	improved	poor absorption
Sprue................	poor absorption	poor absorption	poor absorption
"Intestinal stasis" syndrome...........	poor absorption	poor absorption	improved

SUMMARY

1. Recent advances in the chemistry and physiology of vitamin B_{12} have been briefly reviewed.

2. A modification of Schilling's urinary excretion test was employed in the study of vitamin B_{12} absorption in pernicious anemia and the malabsorption syndrome.

3. A severe defect in vitamin B_{12} absorption was noted in all patients with pernicious anemia which was fully corrected by the addition of intrinsic factor.

4. Deficient vitamin B_{12} absorption was noted in 20 of 25 patients with idiopathic sprue. In addition, 3 patients with a sprue syndrome secondary to the surgical removal of most of the small intestine similarly had defective absorption. Intrinsic factor failed to improve vitamin B_{12} absorption in either group of patients with the malabsorption syndrome.

ACKNOWLEDGMENT

The authors are grateful for the valuable technical assistance of Mrs. Jane Tuck, Mrs. Hazel Weill and Mrs. Maria Yarosh. In addition, we wish to thank Mrs. Ida Nachbar for her help in preparing the manuscript. We are indebted to Dr. Louis R. Wasserman for his guidance in the establishment of the radioactive isotope methods employed in this study.

REFERENCES

1. Castle, W. B., Rhoads, C. P., Lawson, H. A., and Payne, G. C.: Etiology and Treatment of Sprue. Arch. Int. Med., 56: 627, 1935.
2. Spies, T. D., Suarez, R. M., Lopez, G. G., Milanes, F., Stone, R. E., Toca, R. L., Aramburu, T., and Kartus, S.: Tentative Appraisal of Vitamin B_{12} as a Therapeutic Agent. J.A.M.A., 139: 521, 1949.
3. Campbell, D. C., Hall, B. E., and Morgan, E. H.: The Treatment of Pernicious Anemia and other Macrocytic Anemias with Vitamin B_{12}. Med. Clin. N. Amer., 34: 1197, 1950.
4. Diez Rivas, F., Suarez, R. M., Hernandez Morales, F., and Perez Santiago, E.: The Oral Administration of Vitamin B_{12} inTropical Sprue. Ann. Int. Med., 36: 583, 1952.
5. Mollin, D. L., and Ross, G. I. M.: Vitamin B_{12} Deficiency in the Megaloblastic Anemias. Proc. Roy. Soc. Med., 47: 428, 1954.
6. Glass, G. B. J., Boyd, L. J., Gellin, G. A., and Stephanson, L.: Uptake of Radioactive Vitamin B_{12} by the Liver in Humans: Test for Measurement of Intestinal Absorption of Vitamin B_{12} and Intrinsic Factor Activity. Arch. Biochem. and Biophysics, 51: 251, 1954.

7. Glass, G. B. J.: Intestinal Absorption and Hepatic Uptake of Vitamin B_{12} in Diseases of the Gastrointestinal Tract. Gastroenterology, 30: 37, 1956.
8. Reisner, E. H., Jr., Rosenblum, C., and Morgan, M. C.: Urinary Excretion of Orally Administered Co^{60}-Labelled Vitamin B_{12} in Normal Subjects and Patients with Pernicious Anemia and Sprue. Clin. Res. Proc., 2: 56, 1954.
9. Reisner, E. H., Jr., Gilbert, J. P., Rosenblum, C., and Morgan, M. C.: Applications of the Urinary Tracer Test (of Schilling) as an index of Vitamin B_{12} Absorption. Amer. J. Clin. Nutrition, 4: 134, 1956.
10. Krevans, J. R., Conley, C. L., and Sachs, M.: Influence of Certain Diseases on the Absorption of Vitamin B_{12} from the Gastrointestinal Tract. J. Clin. Invest. 33: 949, 1954.
11. Best, W. R., White, W. F., Louis, J., and Limarzi, L. R.: Experiences with the Schilling Test using Co^{60}-Labeled Vitamin B_{12} in Pernicious Anemia, Sprue and other Conditions. J. Lab. and Clin. Med. 44: 767, 1954.
12. Turnbull, A.: Experiences with Labelled Vitamin B_{12}. Proc. Roy. Soc. Med., 47: 424, 1954.
13. Callender, S. T., and Evans, J. R.: Observations on the Relationship of Intrinsic Factor to the Absorption of Labeled Vitamin B_{12} from the Intestine. Clin. Sc. 14: 387, 1955.
14. Halsted, J. A., Marian, S. E., Lewis, P. M., and Gasster, M.: Mechanisms Involved in the Development of Vitamin B_{12} Deficiency. Gastroenterology, 30: 21, 1956.
15. Rickes, E. L., Brink, N. G., Koniuszy, F. R., Wood, T. R., and Folkers, K. Crystalline Vitamin B_{12}. Science, 107: 396, 1948.
16. Rickes, E. L., Brink, N. G., Koniuszy, F. R., Wood, T. R., and Folkers, K. Comparative Data on Vitamin B_{12} from Liver and from a New Source, Streptomyces griseus. Science, 108: 634, 1948.
17. Chaiet, L., Rosenblum, C., and Woodbury, D. T.: Biosynthesis of Radioactive Vitamin B_{12} Containing Co^{60}. Science, 111: 601, 1950.
18. Hodgkin, D. C., Pickworth, J., and Robertson, J. H.: Structure of Vitamin B_{12}: The Crystal Structure of the Hexacarboxylic Acid derived from B_{12} and the Molecular Structure of the Vitamin. Nature, 176: 325, 1955.
19. Hodgkin, D. C., Kamper, J., Mackay, M., and Pickworth, J.: Structure of Vitamin B_{12}. Nature, 178: 64, 1956.
20. Smith, E. L., quoted by Kon, S. K.: The Biochemistry of Vitamin B_{12}. Cambridge University Press, London, 1955, p. 28.
21. Ross, G. I. M., Mollin, D. L., Cox, E. V., and Ungley, C. C.: Hematologic Responses and Concentration of Vitamin B_{12} in Serum and Urine following Oral Administration of Vitamin B_{12} without Intrinsic Factor. Blood, 9: 473, 1954.
22. Unglaub, W. G., Rosenthal, H. L., and Goldsmith, G. A.: Vitamin B_{12} in Blood and Urine after Oral and Parenteral Administration. Federation Proc., 12: 432, 1953.
23. Baker, S. J., and Mollin, D. L.: The Relationship between Intrinsic Factor and the Intestinal Absorption of Vitamin B_{12}. Brit. J. Haemat., 1: 46, 1955.
24. Glass, G. B. J., Boyd, L. J., and Stephanson, L.: Intestinal Absorption of Vitamin B_{12} in Man. Science, 120: 74, 1954.
25. Booth, C. C., and Mollin, D. L.: Plasma, Tissue and Urinary Radioactivity after Oral Administration of Co^{56}-Labelled Vitamin B_{12}. Brit. J. Haemat., 2: 223, 1956.
26. Pitney, W. R., Beard, M. F., and van Loon, E. J.: Observations on the Bound Form of Vitamin B_{12} in Human Serum. J. Biol. Chem., 207: 143, 1954.
27. Oxenhorn, S., and Estren, S.: Unpublished data, 1956.
28. Glass, G. B. J., Boyd, L. J., and Gellin, G. A.: Surface Scintillation Measurements in Humans of the Uptake of Parenterally Administered Radioactive Vitamin B_{12}. Blood, 10: 95, 1955.

29. Estren, S., and Wasserman, L. R.: Pernicious Anemia. I: Remission by Small Oral Doses of Purified Vitamin B_{12}. Proc. Soc. Exper. Biol. and Med. 91: 499, 1956.
30. Heinle, R. W., Welch, A. D., Scharf, V., Meacham, G. C., and Prusoff, W. H.: Studies of Excretion (and Absorption) of Co^{60}-Labeled Vitamin B_{12} in Pernicious Anemia. Tr. A. Am. Physicians, 65: 214, 1952.
31. Schilling, R. F.: Intrinsic Factor Studies. II: The Effect of Gastric Juice on the Urinary Excretion of Radioactivity after the Oral Administration of Radioactive Vitamin B_{12}. J. Lab. Clin. Med., 42: 860, 1953.
32. Glass, G. B. J.: Uptake of Radioactive Vitamin B_{12} by the Liver: Test for Intestinal Absorption of Vitamin B_{12} and Measure of Intrinsic Factor Activity. Clin. Res. Proc., 2: 32, 1954.
33. Ellenbogen, L., Williams, W. L., Rabiner, S. F., and Lichtman, H. C.: An Improved Urinary Excretion Test as an Assay for Intrinsic Factor. Proc. Soc. Exper. Biol. and Med., 89: 357, 1955.
34. Callender, S. T., and Evans, J. R.: The Biochemistry of Vitamin B_{12}, Cambridge University Press, London, 1955, p. 68.
35. Marshak, R. H., Wolf, B. S., and Adlersberg, D.: Roentgen Studies of the Small Intestine in Sprue. Am. J. Roentgenol., 72: 380, 1954.
36. Glass, G. B. J., Boyd, L. J., and Stephanson, L.: Intestinal Absorption of Vitamin B_{12} in Humans as Studied by Isotope Technic. Proc. Soc. Exper. Biol. and Med., 86: 522, 1954.

THE PANCREATIC SECRETION IN THE MALABSORPTION SYNDROME AND RELATED MALNUTRITION STATES

DAVID A DREILING, M.D.

New York, N. Y.

Despite great strides made by the application of esoteric biochemical methods, the physiology of the digestion and absorption of foodstuffs is not completely understood. Defective absorption of aliments in the small intestines may be due to a number of factors: 1. ingested agents antagonistic to the absorption of specific nutriments; 2. deficiency of enzymes necessary to degrade the food to the state in which it can be absorbed, e.g. pancreatic enzyme deficiency; 3. deficiency of adjuvant digestive juices whose absence interferes with the completeness of enzymatic digestion and emulsification, e.g. deficiency of bile or hydrochloric acid; 4. inadequacy of digestion time as seen in patients with rapid intestinal transit; 5. inadequacy of intestinal absorption surface as occurs in patients with massive small intestinal resection or bypass; 6. disruption of the processes whereby the foodstuffs actually pass from the intestinal lumen into the blood stream and lymphatics due, for example, to gross pathology of the small intestines as in widespread inflammatory disease, neoplastic infiltration (lymphosarcoma) and lymphatic blockade (Whipple's disease) or to undiscernible pathologic changes in the small intestines. This latter type of idiopathic malabsorption must be presumed to be caused by various vitamin, protein, or other deficiency states. The various pathogenetic factors are by no means independent. Indeed, the malabsorption state is usually of complex etiology, the extent of its complexity being realized only when the patient is subjected to the most careful physiologic studies.

This report is an analysis of the external pancreatic secretory function in the malabsorption syndrome (idiopathic sprue) and in other states characterized by malnutrition and malabsorption. The material is taken from a series of over 1500 patients studied with the secretin test technique (1). The grouping of cases is in accordance with the diagnosis upon discharge from the hospital.

METHOD

The secretin test is performed upon patients after a 12 hour fast. Under fluoroscopic control, a double-lumened gastroduodenal tube is placed with its tip at the ligament of Treitz. In this position, it is possible with continuous gentle suction to obtain quantitative, uncontaminated duodenal drainage. After an initial control collection period of 20 minutes, 1.0 clinical units of secretin per kilogram body weight is injected intravenously. Thereafter, the duodenal drainage is collected in divided 20 minute specimens for 80 minutes, the interval during which the submaximal stimulation of the pancreas is completely dissipated. The volume, the maximum bicarbonate concentration and the total amylase secretion are obtained in each test. These three factors characterize the pancreatic response to secretin. The diagnostic critical values for volume, bicarbonate and amylase have been

---

From the Department of Chemistry, The Mount Sinai Hospital, New York City.
The secretin used in this study was furnished by the Eli Lilly Company.

obtained from a statistical study of normal subjects (2). They are: 1. volume, 2.0 ml./kg. or more for 80 minutes—average 3.2 ml./kg.; 2. maximum bicarbonate concentration, 90 mEq./L. or more—average 108 mEq./L.; 3. total amylase secretion, 6.0 units/kg. or more for 80 minutes—average 14.2 units/kg.

RESULTS

Two types of pancreatic secretory defect have been described from the secretin responses of patients with pancreatic disease: 1. a quantitative deficiency in which there tends to be a reduction in volume flow with a maintenance of bicarbonate and enzyme secretion—a response characteristic of pancreatic duct obstruction as seen in neoplastic disease (3), and 2. a qualitative deficiency in which the volume secretion is sustained but the bicarbonate response and, to a lesser extent, the enzyme secretion is diminished—a response indicative of chronic inflammatory disease of the pancreas (2).

The results of the study have been summarized in Table I which presents the pancreatic secretion data of patients in whom malnutrition and/or malabsorption has been a clinical problem.

I. Non-Fatty Diarrheas of Various Origins. Patients with persistent, severe, non-fatty, non-bloody diarrheas may be suspected of having pancreatic disease. Sixty-six subjects with such diarrhea were studied. These heterogeneous diarrheas were associated with diabetic neuropathy, mucous colitis, biliary tract pathology, amebiasis, neurosis, or appeared as an isolated symptom. Of the 66 patients with non-fatty diarrheas, 52 had normal pancreatic secretion. Two patients, Cases 1 and 2, disclosed deficient secretion indicative of chronic pancreatic inflammatory disease, i.e. low bicarbonate response (2). Both patients lacked episodes of abdominal pain as well as a definite preceding history of acute pancreatitis. These are examples of the so-called silent or surprise pancreatitis recently stressed by Bartholomew and Comfort (4). There were 12 patients whose secretin test findings, i.e. low volume response, indicated pancreatic neoplasm (3), a diagnosis which in each instance was substantiated at operation. The combination of non-fatty diarrhea, mid-back pain, mild diabetes and weight loss forms a symptom complex most suggestive of carcinoma of the body of the pancreas, the confirmation of which diagnosis is hardly possible in the early stages without secretin test studies.

II. Sprue and Other Forms of Steatorrhea. Ninety patients with steatorrhea were studied. Of these there were 36 patients with the sprue syndrome. Thirty-three patients with sprue had normal pancreatic secretion; three subjects, Cases 3, 4 and 5, had abnormal responses to secretin. There was nothing in the clinical history of these three patients, e.g. duration, severity, or specific symptomatology, which distinguished them from the patients with normal pancreatic secretion. In Case 3 the defect in secretion was extensive, involving marked decreases in volume, bicarbonate and amylase secretion. This patient had a history of celiac syndrome in childhood, indicating the possibility of the malabsorption syndrome in childhood. On the other hand, the marked diminution of volume

TABLE 1

Secretin response data of patients with malabsorption syndromes and malnutrition states. Abnormal values appear in italics.

Diagnosis	Total No. Cases	No. Cases Normal Panc. Secretion	No. Cases Abnormal Panc. Secretion	Secretin Response Data			
				Total volume secretion ml./kg.	Max. HCO_3 secretion mEq./L.	Total amylase secretion u./kg.	Case no.
I. Non-fatty diarrheas	66	52	14				
A. Chronic pancreatitis			2	3.6	*64*	16.6	(1)
				2.3	*78*	8.8	(2)
B. Pancreatic cancer			12				
II. Steatorrheas							
A. Sprue syndrome	36	33	3	*0.5*	*23*	*0.1*	(3)
				3.6	137	*1.8*	(4)
				2.8	*52*	*2.2*	(5)
B. Chronic pancreatitis	9		9				
C. Cystic fibrosis pancreas	3		3				
D. Pancreatic carcinoma	8		8				
E. Diffuse jejuno-ileitis	4	2	2				
F. Organic malabsorption							
1. Massive S.I. resection	3	2	1	2.5	*61*	*4.3*	(6)
2. S.I. lymphosarcoma	4	4					
3. Gastro-ileostomy	2	2					
4. Jejuno-colostomy	4	4					
5. Whipple's disease	1	1					
G. Idiopathic-etiology unknown	14	13	1	2.2	114	*1.8*	(7)
III. Jejuno-ileitis	26	18	8	3.6	96	*2.8*	(8)
				4.2	*42*	*1.9*	(9)
				5.6	95	*2.0*	(10)
				1.2	86	9.2	(11)
				3.2	101	*3.8*	(12)
				2.9	*60*	*4.9*	(13)
				3.8	104	*3.0*	(14)
				2.5	*61*	*4.3*	(15)
IV. Ulcerative colitis	39	35	4	2.1	*50*	10.8	(16)
				1.5	*67*	*0.7*	(17)
				1.6	*71*	7.5	(18)
				0.6	*74*	6.5	(19)
V. Peptic ulcer disease							
A. Gastric ulcer	26	24	2	2.0	*54*	8.9	(20)
				3.2	*42*	*0.7*	(21)
B. Duodenal ulcer	59	54	5	2.5	*48*	11.5	(22)
				2.1	*23*	*0.4*	(23)
				3.3	*73*	18.0	(24)
				1.3	*25*	*0.8*	(25)
				2.9	*28*	6.4	(26)
C. Post-gastrectomy disorders	21	14	7				
1. Dumping syndrome	5	4	1	3.2	*60*	17.9	(27)
2. Pain-diarrhea syndrome	4	2	2	4.1	*59*	*1.2*	(28)
				2.8	*45*	16.2	(29)
3. Steatorrhea syndrome	12	8	4	2.3	*79*	6.3	(30)
				3.2	*41*	9.0	(31)
				3.3	*64*	9.0	(32)
				3.8	*79*	9.5	(33)
D. Post-vagisection	16	16					
NORMAL SERIES	123						
Average				3.2	108	14.2	
Lower Limit Normal				2.0	90	6.0	

secretion suggests the alternate possibility of a mild cystic fibrosis of the pancreas surviving to adolescence.

Fourteen patients with malabsorption syndromes occurring in conjunction with recognizable disease of the small intestines were studied. Three of these were subjects with massive resection of the small intestines. In the two with mesenteric thrombosis and diffuse jejuno-ileitis, the pancreatic secretion was normal. One patient, Case 6, who had had a massive resection for diffuse jejuno-ileitis, displayed marked deficiency in bicarbonate and enzyme secretion as seen in pancreatic fibrosis. There were four patients with malabsorption syndromes due to lymphosarcoma of the small intestines; their pancreatic secretion was normal. In six patients, malabsorption was due to gastro-ileostomy or to jejuno-transverse colostomy. The pancreatic secretion was normal in all six cases. In the patient with Whipple's disease, the pancreatic response to secretin was normal.

The remaining 38 patients with steatorrhea displayed no evidence of absorption defect. There were nine patients with chronic pancreatitis, three with juvenile fibrocystic disease and eight patients with pancreatic cancer. In all these patients, abnormal pancreatic secretion was encountered, the defect varying with the type of pathology present. Six patients with steatorrhea had diffuse jejuno-ileitis; two of these, Cases 9 and 12, disclosed abnormal secretin tests. They are listed with the ileitis patients. There were 14 subjects with steatorrhea in whom no definitive diagnosis was made. Thirteen of these patients had normal secretin tests; one patient, Case 7, showed repeated evidence of an isolated enzyme defect. Isolated enzyme deficiency, i.e. lipase, has been previously reported by Diamond et al. in six of ten patients with idiopathic steatorrhea (5).

Steatorrhea is much more suggestive of pancreatic disease than non-fatty diarrhea. The steatorrhea is the result of a primary pancreatic enzyme deficiency in patients with chronic pancreatitis, fibrocystic disease and pancreatic cancer. In typical sprue and other malabsorption syndromes, the pancreatic secretion ought to be normal (2). Comfort et al. reported 13 patients with the sprue syndrome, in all of whom the secretin test was normal (6). Newsome, however, found two patients with abnormal pancreatic secretion in a series of seven patients with sprue (7). In the present series, three out of 36 patients with sprue had abnormal pancreatic secretion. The changes in secretion noted in these patients are diagnostic of a pancreatic fibrosis, the presence of which in sprue has been indicated by pancreatic pathology observed in post-mortem cases by Adlersberg and Schein (8).

III. and IV. Jejuno-Ileitis and Ulcerative Colitis. The secretin test was done in 26 patients with non-specific inflammatory disease of the small intestines, i.e. regional ileitis or diffuse jejuno-ileitis, and in 39 patients with non-specific inflammatory disease of the colon, i.e. ulcerative colitis. In the patients with ileitis, abnormal pancreatic secretion was encountered in eight subjects, Cases 8 to 15. It is to be noted that the deficiency is almost invariably in the enzyme secretion; three patients, Cases 9, 13 and 15, displayed low bicarbonate values; only one patient, Case 11, had a volume secretory defect. In the 39 patients with ulcerative colitis, abnormal pancreatic secretion was seen in only four, Cases 16 to 19. The deficiency, unlike that in jejuno-ileitis, was not primarily in enzyme secretion.

V. *Peptic Ulcer Disease and Post-Gastrectomy Syndrome.* Data on 85 patients with peptic ulcer disease are presented as a basis for interpretation of the results obtained in the study of 21 patients with post-gastrectomy digestive complaints. Among the 26 patients with gastric ulcer, the pancreatic secretion was normal in 24. Two patients had abnormal secretion suggestive pancreatic inflammatory disease. In these patients, Cases 20 and 21, chronic pancreatitis and pancreatic calcinosis were found at laparotomy. Of the 59 patients with duodenal ulcer, the secretin test findings were normal in 54. Five patients, Cases 22 to 26, showed the abnormal pancreatic secretion seen in chronic pancreatic inflammation.

Of the patients with post-gastrectomy digestive disturbances, intubation of the proximal duodenal loop through the gastroenterostomy was successful in 21 of the 30 patients in whom the secretin test was attempted. The successful intubations included five patients with dumping syndromes, four patients with abdominal pain and diarrhea, and 12 patients with steatorrhea. Evidence of pancreatic deficiency was found in all three groups. One of the five patients with dumping syndrome, Case 27, had test findings indicative of chronic pancreatitis. Two of the patients with pain and diarrhea, Cases 28 and 29, had similar abnormalities. Of the 12 patients with steatorrhea, eight had normal pancreatic secretion; four patients, Cases 30 to 33, had normal enzyme but low bicarbonate responses, an alteration of secretion indicative of pancreatic fibrosis. Sixteen patients with complete vagisection were studied with secretin. The pancreatic response was normal in all cases.

COMMENT

Precise diagnosis of digestive deficiencies requires procedures which evaluate three important variables: 1. the capacity for the production of digestive enzymes, 2. the duration of digestive activity—the intestinal transit time and 3. the capacity for the absorption of foodstuffs. Analysis of stool composition, though of some assistance in the differentiation of enzyme deficiency from absorption defect, is so sensitive to prolongation of transit time that many have raised doubts as to its preciseness as a diagnostic test (9). More reliable procedures include the various digestive tolerance studies. In these, serial determinations in the blood are done after the ingestion of a specific foodstuff and the results are compared with similar determinations made after the oral administration of a split product of that foodstuff. Thus, in the starch tolerance test (10), starch and glucose are given; in a protein tolerance test (11), gelatin and aminoacetic acid are employed; and in the fat tolerance studies (12), butter fat and vitamin A are given.

In the digestive tolerance tests, the absence of a blood response to the foodstuff, e.g. fat, in conjunction with an adequate elevation in the blood following oral administration of the basic substrate, e.g. vitamin A, is indicative of digestive enzyme (pancreatic) deficiency. On the other hand, lack of response to both signifies an absorption defect. Clinical experience has shown that the digestive tolerance tests are more accurate in disclosing defects in absorption than as tests of pancreatic secretory capacity, a conclusion which appears to be equally valid for the newer digestive tolerance studies based upon the detection of radioactive atoms, e.g. I^{131}, in the blood, urine, or stool following the ingestion of an artificially prepared tagged substrate (13, 14). For these reasons complete evaluation of the etiologic factors in the malabsorption syndromes requires study of the external pancreatic secretion with secretin (9).

The frequency of pancreatic secretory deficiencies in patients with non-specific inflammatory disease of the intestines is noteworthy. Among the 26 patients with ileitis, eight patients had abnormal pancreatic secretion. The most consistent defect observed is in the enzyme secretion. In fact, five of these eight patients had isolated enzyme defects. Among the 39 patients with ulcerative colitis, there were four with abnormal secretion. Here the defect was in volume and bicarbonate as well as in enzyme secretion. Ball and others have commented upon the postmortem demonstration of unsuspected pancreatic fibrosis in patients with ileitis and ulcerative colitis (15, 2, 16). In no other group of patients studied with the secretin test has isolated enzyme deficiency been encountered with such consistency as in the patients with ileitis and jejunitis. Although the series is small, it is of interest that the defects in pancreatic secretion noted in the patients with sprue syndrome are similar to those seen in the jejuno-ileitis group, both of which are quite distinct from the more advanced defects observed in those patients with ulcerative colitis who displayed deficient pancreatic secretion. The British have been intrigued by the possibility of an etiologic relationship between sprue and jejuno-ileitis. Brooke, Cooke and Avery-Jones have reported cases of coeliac disease, sprue and idiopathic steatorrhea which have progressed to non-specific inflammatory disease of the intestines (17, 18).

The secretin test results in the cases of ulcerative colitis are in agreement with those reported by Lake (16), but mitigate against the hypothesis advanced by Portis (19, 20), i.e. that the ulceration in ulcerative colitis is due to the excessive proteolytic action of pancreatic ferments on a colonic mucosa rendered sensitive by high lysozyme titre. In none of the patients studied was there any evidence of hypersecretion of pancreatic ferments.

The abnormal pancreatic secretion observed in sprue, ulcerative colitis and jejuno-ileitis, correlated with the post-mortem demonstration of pancreatic fibrosis in these disorders, suggests an underlying nutritional etiology, most likely a protein deficiency state, an etiology of pancreatic fibrosis which has already been reported for other protein deficiency states (21, 22) and in the experimental animal (23, 24).

The development of peptic ulcer in patients with chronic pancreatitis and, particularly, the occurrence of diarrhea, steatorrhea and the dumping syndrome in subjects treated with gastrectomy for ulcer disease has implied to some an etiologic relationship between pancreatic inflammatory disease and the ulcer diathesis. The physiologic basis for such a relationship is clear insofar as the development of ulcer in pancreatitis; for here the absence of the neutralizing effect of the pancreatic juice must result in unopposed duodenal hyperchlorhydria. Such a mechanism may also serve to explain the occurrence of marginal ulcers in patients following a radical resection of the duodenum and pancreatic head. The present series disclosed seven patients with chronic pancreatitis who had duodenal or gastric ulcers. The inverse hypothesis enunciated by Poth (25), viz. that uncomplicated peptic ulceration results from an inadequacy of pancreatic secretion, is not supported by the results of this study in which 78 of 85 subjects with ulcer disease had normal pancreatic secretion.

The digestive disturbances following gastrectomy may, not uncommonly, be due to pancreatic disorders. Vagisection, *per se*, does not appear to alter the pancreatic response to secretin (26), but the possibility exists that shunting the food across the duodenum may invoke a lesser elaboration of secretin than the passage of foodstuffs through this channel. Only a comparative study of patients with Bilroth I and Bilroth II operations can resolve this question.

Of five patients with dumping syndrome, one patient displayed evidence of pancreatic fibrosis. Among the group with persistent pain and diarrhea, two out of four showed evidence of chronic pancreatitis. The post-gastrectomy steatorrheas, which appear to have the laboratory findings of a sprue syndrome but which are refractory to regimens of vitamin B_{12}, folic acid and adrenocortical hormone, may upon investigation disclose evidence of a coexisting pancreatic etiology. One-third of these patients showed a pancreatic secretory defect. Pancreatic involvement may account for the relative refractiveness of the post-gastrectomy steatorrheas to sprue therapies.

CONCLUSIONS

The secretin test is of great value in the study of patients with the malabsorption syndrome and with malnutrition states. It affords a means of differential diagnosis between digestive disorders due to pancreatic secretory deficiency and those due to defective absorption of foodstuffs. In many instances the secretin test findings have indicated that the digestive disturbance is complex, involving both abnormalities of absorption and of pancreatic secretion.

REFERENCES

1. Dreiling, D. A.: Technique of the Secretin Test. J. Mt. Sinai Hosp. 21: 363, 1955.
2. Dreiling, D. A.: Studies in Pancreatic Function V. The Use of the Secretin Test in the Diagnosis of Pancreatitis and in the Demonstration of Pancreatic Insufficiencies in Gastrointestinal Disorders. Gastroenterology 24: 540, 1953.
3. Dreiling, D. A.: Studies in Pancreatic Function IV. The Use of the Secretin Test in the Diagnosis of Tumors in and about the Pancreas. Gastroenterology 18: 184, 1951.
4. Bartholomew, L. G., and Comfort, M. W.: Painless Chronic Pancreatitis. Annual Meeting Am. Gastroenterology Ass., Atlantic City, April 1956.
5. Diamond, J. S., Siegal, S. A., and Myerson, S.: The Secretin Test as an Aid in the Differential Diagnosis of the Steatorrheas with a Report of 14 Cases. Rev. Gastroenterology 7: 429, 1940.
6. Comfort, M. W., Dornberger, G. R., Wollaeger, E. E., and Power, M. H.: External Pancreatic Secretion as Measured by the Secretin Test in Patients with Idiopathic Steatorrhea (Non-Tropical Sprue). Gastroenterology 13: 135, 1949.

7. Newsone, J.: The Secretin Test of Pancreatic Function and its Use in Steatorrhea. Gastroenterologia 74: 257, 1949.
8. Adlersberg, D., and Schein, J.: Clinical and Pathologic Studies in Sprue. J.A.M.A. 134: 1459, 1947.
9. Dreiling D. A., and Janowitz, H. D.: Exocrine Pancreatic Secretion: Effects of Pancreatic Disease. Am. J. Med. 11: 98, 1956.
10. Althausen, T. L., and Uyeyama, K.: A New Test of Pancreatic Function Based upon Starch Tolerance. Ann. Int. Med. 41: 563, 1954.
11. Anfanger, H., and Heavenrich, R. N.: Amino Acid Tolerance Tests in Children. Am. J. Dis. Child. 77: 425, 1949.
12. Adlersberg, D., and Sobotka, H.: Fat and Vitamin A Absorption in Sprue and Jejunoileitis. Gastroenterology 1: 357, 1943.
13. Chinn, A. B., Latvik, P. S., Stitte, R. N., and Buckaloo, G. W.: The Use of I_{131} Labelled Protein in the Diagnosis of Pancreatic Insufficiency. New Eng. J. Med. 247: 877, 1952.
14. Shingleton, W. W., Wells, M. H., Bayling, G. F., Ruffin, J. M., and Saunders, A.: The Use of Radioactive Labelled Protein and Fat in the Evaluation of Pancreatic Disorders. Surg. 38: 134, 1955.
15. Ball, W. P., Baggenstoss, A. H., and Bargen, J. A.: Pancreatic Lesions associated with Chronic Ulcerative Colitis. A.M.A. Arch. Path. 50: 347, 1950.
16. Lake, M., Nickel, W. F., Jr., and Andrus, W. De W.: Possible Role of Pancreatic Enzymes in the Etiology of Ulcerative Colitis. Gastroenterology 17: 409, 1951.
17. Brooke, B. N.: Ulcerative Colitis, p. 6. The Williams & Wilkins Co., Baltimore, 1953.
18. Avery-Jones, F. (Cooke, W. T.) Modern Trends in Gastroenterology, p. 523. Paul B. Hoeber Inc., New York, 1952.
19. Portis, S. A., Block, C. L., and Necheles, H.: Studies on Ulcerative Colitis and on Some Biological Effects of Detergents. Gastroenterology 3: 106, 1944.
20. Portis, S. A.: Idiopathic Ulcerative Colitis: Newer Concepts concerning its Cause and Management. J.A.M.A. 139: 208, 1949.
21. Veghelyi, P. V., Kemeny, T. T., Pozsonyi, J., and Sos, J.: Dietary Lesions of the Pancreas. Am. J. Dis. Child. 79: 685, 1950.
22. Davis, J. N. P.: The Essential Pathology of Kwashiorkor. Lancet 254: 317, 1948.
23. Veghelyi, P. V., Kemeny, T. T., and Sos, J.: Cystic Changes in the Pancreas: Its Experimental Production. Am. J. Dis. Child. 79: 65, 1950.
24. Farber, E., and Popper, H.: Production of Acute Pancreatitis with Ethionine and its Prevention with Methionine. Proc. Soc. Exp. Biol. and Med. 74: 838, 1950.
25. Poth, E. J., and From, S. M.: The Relation of Pancreatic Secretion to Peptic Ulcer Formation. Gastroenterology 16: 490, 1950.
26. Dreiling, D. A., Druckerman, L. J., and Hollander, F.: The Effect of Complete Vagisection and Vagal Stimulation on Pancreatic Secretion in Man. Gastroenterology 20: 578, 1952.

PATHOLOGIC STUDIES IN IDIOPATHIC SPRUE

HILLARD W. HIMES, M.D.
AND
DAVID ADLERSBERG, M.D.
New York, N. Y.

According to most observers there are no characteristic gross pathologic changes in primary sprue, whereas organic disease (e.g. lymphosarcoma, amyloidosis, Whipple's disease, etc.) is responsible for the malabsorption syndrome found in secondary sprue.

In the broader concept of idiopathic sprue, the disorder is considered to be a genetically-transmitted metabolic error, the focal point of which is intestinal malabsorption. According to this concept celiac disease in children, tropical and non-tropical sprue (idiopathic steatorrhea) are thought to be clinical manifestations of the same metabolic disorder triggered by a number of environmental factors such as infection, malnutrition or stress of tropical climates (1). One of the early observers of the disease, Samuel Gee in 1888, stated that "naked eye examination of dead bodies throws no light on the nature of the celiac affection" (2). Thaysen (3) believed that certain changes seen at autopsy in sprue patients could be attributed to post-mortem alteration, since the intestinal mucosa of sprue patients appears to be unusually susceptible to autolytic change. Adlersberg and Schein (4) in their study of six autopsied cases of primary sprue observed that several anatomical findings, while not necessarily characteristic or pathogenetically significant, were encountered at autopsy in cases of sprue. Atrophy of the small intestinal mucosa and villous deformities consisting of flattening and blunting of the villi (clubbing) as well as increased cellularity of the lamina propria were noted. The deformities of the villi were in one instance associated with stromal hyaline band formation near the tips of the villi (Schein (5)). These authors further describe instances of hemofuscinosis of the muscularis of the gastrointestinal tract, chronic mesenteric lymphadenitis with replacement of lymphatic tissue by hyaline and fibrous bands, centrolobular fibrosis of the liver and various degrees of pancreatic fibrosis (in the absence of biliary disease). Although it was apparent that these changes in the bowel and mesenteric lymph nodes were such as to impair absorption, the more fundamental pathogenetic implications were not clear.

Oehler (6) described the clinical and anatomical findings in seven patients with sprue, of whom four were considered to have idiopathic sprue. In this latter group there were marked changes in the small bowel consisting of chronic inflammation, ulceration, and fibrosis of the submucosa Similar but somewhat less intense changes were seen in the colon. Some of the cases showed "severe nephrosis". Unfortunately, these cases are not too well documented as sprue in that there were no quantitative fat analyses of the stool and no absorption

---

From The Department of Medicine, The Mount Sinai Hospital, New York City.

studies reported. Similar small bowel changes have been previously described in patients with primary sprue (7, 8, 9).

The utilization of biopsy techniques in living patients has permitted more detailed histological observation of the small bowel since rapid post-mortem autolysis causes changes which defy interpretation. Milanes et al. obtained a surgical biopsy of the jejunum in a case of tropical sprue in relapse (10). These authors observed atrophy of the villi and glands, increased cellular infiltration of the lamina propria and thickening of Auerbach's plexus. Paulley, utilizing surgical biopsies of the jejunum and mesenteric lymph nodes in patients with idiopathic steatorrhea, observed somewhat similar deformities of the villi and cell infiltration of the lamina propria (11). Butterworth has obtained a number of surgical jejunal biopsies in patients with tropical sprue at the time of operation for other disease (12). Atrophy of mucosa, clubbing of villi and increase of round cells and eosinophils of the submucosa were found in greater or lesser degree in these patients. Shiner has modified the Wood technique for obtaining gastric biopsies for duodenal and jejunal biopsies (13). This procedure appears to be a safe and clinically approved method for obtaining biopsies of jejunal mucosa. Her studies in sprue patients will be discussed elsewhere in this symposium (14).

The material of the present study includes 11 autopsies of patients with idiopathic sprue whose diagnosis was established by clinical and laboratory criteria. Six of these cases have been included in a previous report (4). In addition, jejunal biopsy material obtained by Dr. Margot Shiner, utilizing her jejunal biopsy technique from living sprue patients, is compared with the autopsy material.

CASE REPORTS

Case 1

A 48 year old Puerto Rican female was hospitalized in April 1931 with a four month history of weight loss, vomiting, diarrhea and fever. Her temperature was 103°F. The mouth was sore and the tongue was ridged. There were hemorrhages in both fundi. The liver and spleen both were palpated four fingers below the costal margins. Hemoglobin was 25 per cent, RBC 1.2 million per cu. mm., WBC 2500 per cu. mm. There was erythroid hyperplasia of the bone marrow. Following a blood transfusion, the temperature fell and vomiting and diarrhea ceased. Blood Wassermann and Kahn tests were four plus. Dysentery and typhoid-paratyphoid agglutinations were negative. Stool culture revealed *B. coli* and enterococcus. There was 13.5 per cent fat in the stool (low fat diet). Blood calcium was 8.5 mg. per cent. Free acid was present in the gastric contents. Liver extract and antiluetic therapy were given. Reticulocytes rose from 2 to 21 per cent in two weeks. There was a gain of 15 pounds in body weight during hospitalization.

She was then well until 24 hours before her last admission in September 1933, when she developed generalized abdominal pains, nausea and vomiting. There was no diarrhea. The abdomen was rigid throughout. Tenderness was most pronounced in the right lower quadrant. Blood examination showed WBC 4,200 per cu. mm. with 43 per cent polymorphonuclear cells, hemoglobin 49 per cent, RBC 2.25 million per cu. mm. At operation an acute appendicitis was found. There was no evidence of peritonitis. Post-operatively, the patient developed fever and signs suggesting bronchopneumonia. Despite oxygen and digitalization, the patient became increasingly dyspneic and expired on the third post-operative day.

Post-mortem examination revealed moderate generalized abdominal distention. There was a herniated segment of transverse colon immediately beneath the appendectomy wound. There was 1000 ml. of this dark amber fluid in the peritoneal cavity. The small intestine was collapsed. The cecum and part of the transverse colon were distended.

The heart weighed 300 gm. There were a few small areas of fatty changes as well as minimal perivascular fibrosis. The combined weight of the lungs was 640 gm. The bronchi and bronchioles were filled with a tenacious thick red mucous. The liver weighed 1920 gm and had a greasy feel. Microscopically, there was fatty vascuolization in the mid-periphery of many lobules. The spleen weighed 490 gm. The cut surface was reddish-grey, firm and dry with prominent white pulp and trabeculae. Microscopically, the follicles were numerous. The pulp was congested and there was an increase in the reticulum and connective tissue throughout. The pancreas was normal. The kidneys together weighed 380 gm. There was slight congestion of the vessels. There was central autolysis of the adrenals. There was mild congestion of the esophagus. The gastric mucosa was atrophic. Microscopically, there was autolysis and atrophy of the glands. There was some increase in the mononuclear and plasma cells of the lamina propira. No information on the remainder of the intestines is available (autolysis).

Cause of death. Acute appendicitis.

Case 2

A 41 year old white female was hospitalized in July 1935 because of weakness, dyspnea on exertion and ankle edema of 3 months' duration. She had a history of celiac disease in childhood with diarrhea (5 to 6 stools daily) continuing all of her life. Examination revealed a deformed rachitic dwarf weighing 54 pounds. There was hemorrhagic retinitis, pallor and petechiae of the skin, smooth tongue, hepatomegaly and tenderness of all bones. Hemoglobin was 14 per cent (Sahli), RBC 820,000 per cu. mm., WBC 1950 per cu. mm. Bone marrow showed erythroid hyperplasia. Total protein was 5.7 gm. per cent. Serum calcium was 7.6 mg. per cent. Glucose tolerance test (oral) revealed a flat curve. Stool fat was 12.5 per cent of the dry stool weight (low fat diet). Treatment with iron, liver extract and transfusions resulted in improvement of all symptoms including diarrhea. Her symptoms gradually recurred however, and she was readmitted to the hospital two months later. A gastrointestinal x-ray series showed distention of the small bowel and no other changes. Hemoglobin was 42 per cent. Blood transfusions were given and again resulted in improvement. At the time of discharge the hemoglobin was 72 per cent.

She was rehospitalized two days after discharge because of onset of vomiting of bright red blood, epistaxis and bleeding gums. Examination revealed carpo-pedal spasm, positive Chvostek and Trousseau signs, a large hematoma of the left buttock and thigh, ecchymoses, petechiae and bleeding gums. Hemoglobin was 46 per cent, RBC was 2,080,000 per cu. mm., bleeding time was 5½ minutes, clotting time was 29 minutes. The diffuse severe hemorrhages could not be controlled with transfusions and calcium gluconate. After 10 days her temperature suddenly rose to 105°C. and she expired.

Post-mortem examination revealed numerous ecchymoses of the skin and multiple hemorrhages into the pleura, peritoneum, mucous membranes, anterior mediastinum and renal pelvis. The heart weighed 165 gm. The liver weighed 1240 gm. and showed some fatty changes. The pancreas revealed a small amount of interlobular fibrosis. The spleen weighed 150 gm. There was active hyperemia and hyperplasia of the lining epithelium of the sinusoids. The adrenals were normal. The kidneys weighed 220 gm. together. There was a diffuse pyelonephritic scarring. The esophagus was normal. The mucosa of the stomach was grossly flat and pale. The small intestine showed frequent areas of congestion. The duodenal mucosa was normal. The smooth nuscle fibers of the muscularis contained large numbers of coarse, yellow-brown pigment granules which were distributed throughout the sarcoplasms. They did not give a positive reaction for iron. A similar but less marked granularity was seen in the muscularis of the jejunum and ileum. The remainder of the alimentary tract was without significant alteration.

The bone marrow was grossly spongy and red. Microscopically, there was a decided erythroid hyperplasia. The parathyroid glands were normal. The skin revealed a brown-green pigment in the basal layers of the epidermis. This pigment gave a negative reaction for iron.

Cause of death. Multiple hemorrhages.

Case 3

A 16 year old white male was admitted 10/30/43 for the first time because of abdominal pain and diarrhea of 3 months' duration. Because of persistence of abdominal pain, an exploratory laporatomy was performed. Enlarged hyperplastic mesenteric lymph nodes were the only abnormal findings. Hypoproteinemia, flat glucose and vitamin A tolerance curves and lymphocytosis of 65 per cent were discovered. Small intestinal series revealed segmentation of barium. Therapy including 2 transfusions, liver extract and vitamins resulted in some improvement although diarrhea (1 to 2 times daily) persisted. Four months prior to his final admission (7/8/44), he again began to vomit. Vomitus became coffee-ground in character and he suddenly became delirious and comatose on the day of admission. Examination revealed positive Trousseau's sign and convulsive movements of the body. There was bleeding from the mouth and rectum. Calcium was 5.5 mg. per cent. Bleeding time was over 20 minutes and clotting time was 15 minutes. Prothrombin index was less than 3 per cent of normal. Cephalin flocculation test was four plus. There was slight scleral icterus. The stool was grossly bloody and contained moderate numbers of fatty acid crystals. Coma rapidly deepened and the patient expired on the second hospital day.

Post-mortem examination revealed the body to be poorly nourished. There were numerous ecchymoses. The panniculus was brownish-yellow and thin. The stomach was markedly dilated. The small intestine and transverse colon were dilated. The mesenteric lymph nodes are moderately enlarged and soft. The heart weighed 175 gm. and was somewhat flabby. The lungs weighed 560 gm. There was generalized hyperemia. The liver weighed 1100 gm. and was quite soft. Section revealed a pattern in which the yellow periportal areas formed a slightly elevated rim above the dark red intervening areas. The parenchyma was friable. Microscopically, there was an extensive and severe parenchymal degeneration in which the dissociation of liver cells was striking. The individual cells were generally small and spindle-shaped. Many fat droplets were present. Mitotic figures were frequent at the periphery of the lobule. There was a striking infiltration of small round cells in these areas. The pancreas was normal grossly. There was some acinor atrophy. The spleen weighed 210 gm. There was marked congestion. The adrenals were normal. The right kidney weighed 200 gm. and the left 160. They were somewhat pale in color. The entire gastrointestinal tract contained blood. The esophagus was normal. The mucosa of the stomach and small intestines was atrophic, smooth and tan-colored. Microscopic examination of the stomach revealed slight atrophy and a mild infiltration of round cells in the mucosa and submucosa. The small intestinal villi were broad and clubbed. There were band-like deposits of hyaline material at the villous tips just beneath the basement membrane. There was a moderate polymorphonuclear leucocyte and eosinophil infiltration in the submucosa. The large intestine was not abnormal. The mesenteric nodes were normal. The bone marrow was normal except for some increase in fat. The pituitary was normal. The parathyroids were congested and hemorrhagic. The skin revealed an increase in the melanin-bearing chromatophores in the basal layers.

Cause of death. Liver necrosis and multiple hemorrhages.

Case 4

A 32 year old white female was observed at The Mount Sinai Hospital for a period of 12 years prior to her death. Her original admission at the age of 20 was for edema, associated with hypoproteinemia and hypocalcemia. A gastrointestinal series was interpreted as negative. One year later she was readmitted because of severe diarrhea. Gastric achlorhydria, hypoproteinemia and a flat oral glucose tolerance curve were found. At the age of

30 she had an attack of jaundice and fever. At the age of 31, she was again hospitalized for extreme weight loss, diarrhea and tetany. Steatorrhea (21.4 per cent of dry stool weight), flat vitamin A tolerance tests and hypoproteinemia were found. She was hospitalized for the last time in July 1944 for diarrhea, tetany and weight loss. Blood pressure was 120/86. Chvolstek's and Trousseau's signs were present. The patient was poorly nourished. Hemoglobin was 80 per cent. A small bowel roentgen study revealed marked dilatation, segmentation of barium and hypersecretion. ECG showed myocardial involvement. Extrasystoles developed after I.V. calcium therapy. The serum albumin was 2.5 gm. per cent; globulin, 1.5 gm. per cent; Ca, 8 mg. per cent; P, 4.0 mg. per cent; alkaline phosphatase, 31 K-A units. Treatment consisted of liver extract, vitamins, adrenal cortical extract, transfusions, pancreatin, dihydrotachysterol and calcium gluconate. One day prior to her death, she developed a sore throat. On the final day of her life, she became stuporous. The blood pressure was unobtainable. Tetanic contractions, foaming at the mouth and involuntary defecation preceded death.

Post-mortem examination revealed the body to be extremely emaciated. The heart weighed 180 gm. The myocardium was brown and flabby. The lungs weighed 360 gm. There was focal emphysema and atelectasis. The liver weighed 2080 gm. The organ was yellow in color and greasy. There was a large amount of brown pigment in the Kupfer cells. The spleen weighed 75 gm. There was some degree of fibrosis microscopically. The pancreas was somewhat enlarged. There was a fine fibrosis throughout. The adrenals were normal. The kidneys were normal and of equal size (210 gm.). The esophagus was narrow and the stomach contracted and small. The gastric mucosa was atrophic. There was a submucous infiltration of round cells in the distal esophagus. There was a small myoma in the stomach. The small intestine appeared normal in every respect. There were two subserosal chondromas in the jejunum. The colon was normal. The mesenteric nodes were normal. Examination of the parathyroids revealed a conspicuous amount of connective tissue invading the parenchyma. The bone marrow was somewhat fatty. Examination of the brain revealed thrombosis of the superior sagital sinus and cerebral veins.

Cause of death. Marantic thrombosis of dural sinus and cerebral veins.

Case 5

A 53 year old male was hospitalized on 4/21/46 because of low abdominal pain of six hours duration. He had been hospitalized two years previously because of diarrhea of 14 years' duration, carpo-pedal spasms and weight loss. Hypoproteinemia, hypocalcemia, flat vitamin A tolerance curve and barium meal studies consistent with diagnosis of sprue were found at that time. Treatment consisted of liver extract, vitamins, calcium and low fat diet and resulted in improvement. For four months prior to his final admission, he had symptoms of subacute obstruction of the large bowel. For the six hours prior to admission, he had severe lower abdominal pain, nausea and vomiting. Examination revealed a severely emaciated man in acute distress. There was marked abdominal distention and absent bowel sounds. There was marked clubbing of fingers. The hemoglobin was 61 per cent with 2450 WBC per cu. mm. The specific gravity of the urine was 1.005 with 1+ albumin and 4+ sugar. X-rays revealed obstruction of the large bowel. One day after admission, an operation was performed. A sigmoid volvulus was discovered. Sigmoidectomy and cecostomy were performed. Twelve days post-operatively urinalysis revealed many red blood cells. Seventeen days post-operatively the patient was catheterized because of bladder distention and regular catheterization was required for the remainder of his hospitalization. Temperature varied between 98 and 103.2°F. His course was progressively downhill with abdominal distention, cachexia, mental dullness, apathy and hallucinations. Urine revealed 5 to 12 red and white blood cells, a few granular casts and a trace of albumin. Patient expired 25 days post-operatively.

Post-mortem examination revealed numerous adhesions between loops of small intestine and abdominal wall. The abdominal contents were matted together. There was no excess of peritoneal fluid. There was dilatation of the stomach and small intestine. The dilatation was massive in the stomach and proximal jejunum but decreased distally. A cecostomy was found in the right lower quadrant. The sigmoid colon had been resected. The mesentery contained numerous, soft, pale brown lymph nodes, the largest of which was 2 cm. in diameter. The heart weighed 300 gm. There was some atrophy of the myocardial bundles and minimal myocardial fibrosis. The lungs together weighed 2075 gm. They were heavy and darkened throughout. There was a severe generalized hyperemia and intra-alveolar hemorrhage. There were focal areas of bronchopneumonia. The liver weighed 1875 gm. and showed central lobular congestion. There was a fine diffuse intralobular fibrosis of the pancreas. The spleen weighed 190 gm. There was marked congestion of the pulp and sinusoids. The adrenals were of average size and showed diffuse post-mortem autolysis. The surface of the kidneys was studded with small, soft, yellow elevations with thin hemorrhagic margins. There were many yellow streaks throughout the cortex and medulla and a number of small abscesses. Microscopically, there was acute pyelonephritis with abscess formation.

The wall of the esophagus was diffusely edematous. There was a severe acute ulcerative esophagitis. There was hemofuscin pigmentation of the smooth muscle. The gastric mucosa was grossly normal but revealed microscopic evidence of hyperemia and acute inflammation of the lamina propria and pigmentation of the muscularis. There was a distinct gross pigmentation of the small and large bowel directly beneath the serosa. This pigmentation was diffusely present but was not as intense in the ileum. The duodenum revealed microscopic evidence of acute inflammation of the submucosa. There was blunting of the villi of the jejunum and ileum. There was a diffuse hemofuscinosis of the muscularis mcuosa in the entire small bowel and colon. There was an acute necrotizing proctitis. The bone marrow was hyperplastic. The skin revealed a diffuse grey-tan pigmentation. There were a moderate number of large cells containing much brown granular pigment. Some cells gave a positive staining reaction for iron and others for hemofuscin.

Cause of death. Volvulus of the sigmoid with resection; acute pyelonephritis with abscess formation.

Case 6

A 53 year old white female was admitted for the first time in 1937 because of severe anemia and diarrhea. The hemoglobin was 23 per cent with 1.7 million RBC per cu. mm. Splenomegaly, achlorhydria and koilonychia were found. Transfusions and iron and hydrochloric acid therapy restored the hemogram to normal. A diagnosis of achlorhydric hypochromic microcytic anemia was made. She was then well until six months prior to her second admission in 1943 when she developed diarrhea, weakness and weight loss. Hepatosplenomegaly and bleeding hemorrhoids were found. The hemoglobin was 59 per cent with 4.4 million RBC per cu. mm.; the glucose tolerance curve was flat. A diagnosis of nontropical sprue and chronic blood loss from bleeding hemorrhoids was made. Hemorrhoidectomy was subsequently performed. She was admitted for the fourth time in 1945 because of recurrence of severe diarrhea (8 to 10 times daily). Stools were repeatedly positive for occult blood. The serum Ca was 7.4 mg. per cent; vitamin A and glucose tolerance curves were flat. The stool contained fat and undigested food particles. She responded to treatment consisting of pancreatic extract, blood transfusions and I.V. Amigen. Forty-eight hours before her final admission in November 1945 she developed a dry cough. The following day she noted fever and dyspnea. On the day of admission she became cyanotic, extremely dyspneic and stuporous with temperature of 104°F. There was a loud inspiratory stridor with inspiratory retraction of the supraclavicular regions. Bronchoscopy revealed laryngeal and tracheal edema. The patient improved markedly after this procedure only to have another attack of laryngeal edema and expire suddenly.

Post-mortem examination revealed extensive edema and congestion of the lungs with a small area of bronchopneumonia in the right upper lobe. The bronchial mucosa was reddened. There was marked laryngeal edema. The tracheal mucosa was deep red with greyish areas of surface necrosis. Microscopically throughout the lung there was a widespread exudate of blood and large mononuclear elements. There was a perivascular and peribronchial cuffing of round cells and leucocytes. The bronchial epithelium was almost completely missing. The heart weighed 300 gm. Its muscle was brown and showed areas of fibrosis and lipomatosis. The liver weighed 1580 gm. and had a normal consistency. There were many leucocytes in the periportal spaces. The spleen weighed 300 gm. and was coarsely lobulated. The cut surface revealed a congested pulp with discernible landmarks. The pancreas showed scattered intralobular fibrosis. Examination of the adrenals revealed some central autolysis. The kidneys weighed 350 gm. There was sclerosis of the larger renal arteries. The bone marrow was normal.

The stomach and intestines were markedly dilated. The esophagus was normal. The stomach showed a mucosal polyp the size of a pea near the pylorus. The mucosa of the small and large bowel was normal in every respect grossly. The mucosa of the antrum and fundus was slightly lower than normal. There were many plasma cells and leucocytes in the lamina propria. In the small intestine, there was a slight increase of plasma cells and polymorphonuclears in the lamina propria. There were a number of enlarged lymph nodes in the mesentery. Microscopically there was a diffuse fibrosis of these nodes.

Cause of death. Acute necrotizing laryngotracheitis (influenza virus B).

Case 7

A 59 year old white female was hospitalized in July 1950 because of diarrhea, gaseous eructations and abdominal bloating. Five years previously she began to suffer from nausea and vomiting associated with a 50 pound weight loss. Cholecystectomy was performed in 1947. Following this procedure, she was somewhat improved but still had frequent eructations, bloating and bouts of vomiting. She had had chronic bronchitis with a cough productive of mucopurulent sputum for many years. Vomiting was usually preceded by coughing and gagging. Four months prior to admission her symptoms became somewhat more severe and were now associated with diarrhea (10 to 12 watery, light-yellow stools daily). The blood pressure was 115/75. Wheezes were heard throughout the chest with some prolongation of the expiratory phase. There was a grade III precordial murmur heard best at the apex. The liver was felt one finger's breadth below the right costal margin. There was clubbing of the digits. The hemoglobin was 11 gm. per cent; WBC 9,800 per cu. mm. Congo red test was negative. The total proteins were 4.8 gm. per cent with albumin 2.2 and globulin 2.6 gm. per cent. Stools contained 45 per cent fat, mainly fatty acids with some neutral fat. Prothrombin time was 23 seconds. The blood calcium was 6.4 mg. per cent. Pancreatic function studies were normal. Gastrointestinal x-ray series showed a normal stomach and duodenum. There was flocculation and segmentation of barium in the small bowel. Vitamin A tolerance tests done before and after the administration of cortisone and ACTH revealed a flat curve. An oral glucose tolerance test revealed a flat curve, whereas the intravenous glucose tolerance test was normal. Therapy, consisting of high caloric-low fat diet, vitamins, liver extract and cortisone (100 mg. daily for 15 days), did not alter the clinical course. ACTH, given intramuscularly for 15 days, likewise did not produce significant benefit. She developed abscesses of the buttocks at the sites of ACTH injections. These were drained and the patient was discharged. Two weeks later she was admitted to another hospital because of marked exacerabation of diarrhea, vomiting and weight loss. She developed a lobular pneumonia while hospitalized. In spite of all therapy, the patient's course was progressively downhill and she expired on February 21, 1951.

Post-mortem examination revealed the body to be markedly emaciated. The panniculus was minimal in amount. There was a large area of consolidation in the left lower lobe and smaller areas in the right upper and lower lobes. There was calcification of the mitral ring and the aortic cusps with stenosis of the aortic valve. The liver was of average size and appeared grossly normal. The pancreas was small and somewhat fibrotic. The spleen, kidneys and adrenals were grossly normal. The stomach was markedly dilated with thin but intact mucosa. The duodenum was markedly dilated and had a pale greyish-white mammilated mucosa. There were many various sized irregular areas which were hemorrhagic and possibly superficially ulcerated. The remainder of the small intestine was normal. The mesenteric lymph nodes were greatly enlarged, soft, pale yellowish-pink in color. The mucosa of the large intestine was intact and for the most part thin and atrophic. In the transverse colon, the mucosa was irregular in thickness and often granular in appearance.

Microscopic examination revealed confluent lobular pneumonia, fatty degeneration of the myocardium, fatty infiltration and cloudy swelling of the liver and acute splenitis. There was atrophy of the mucosa of the stomach. The duodenal mucosa revealed several areas of superficial necrosis affecting only part of the folds or glands in most places. In a few, however, the mucosa was destroyed for its entire thickness, the bare submucosa covered with fibrin enmeshing cellular debris. In none of these areas was any inflammatory reaction or cellular infiltration of the supporting stroma noted. The submucosa was rich in distended and congested blood vessels. There were several small areas of superficial necrosis in the ileum with evidence of cellular reaction. The mucosa was atrophic throughout both ileum and colon. The normal architecture of the mesenteric nodes was preserved. The sinusoids were dilated and filled with large and small lymphocytes and desquamated epithelial cells. The follicles were large and numerous with prominent germinal centers.

Cause of death. Confluent bronchopneumonia, emaciation.

Case 8

A 38 year old white female was hospitalized for the third time in January 1951, because of diarrhea of one month's duration. She was first hospitalized at the age of 28 in 1934 because of diarrhea, abdominal distention and weight loss. Findings at that time included a fecal fat of 48 per cent. There was generalized osteoporosis. Gastrointestinal x-ray study was interpreted as showing a masked diffuse inflammatory process in the lower jejunum and entire ileum. She developed a Brown-Sequard syndrome at D_{10-11}. The cause of this neurological complication, which cleared spontaneously, was not ascertained. Treatment resulted in some improvement in the sprue syndrome. She was again hospitalized in 1943 because of exacerbation of symptoms. Treatment with a high calorie-low fat diet, vitamins and liver extract resulted in a marked improvement. One month prior to her final admission, symptoms again became severe. On examination, she was emaciated and chronically ill. The abdomen was distended and thin-walled with visible peristalsis. There was clubbing of the digits. An oral glucose tolerance test revealed a flat curve. A gastrointestinal x-ray series revealed dilated loops of small intestine with thickening of mucosal folds, segmentation and flocculation of barium and prolonged transit time. She was persistently nauseated with frequent vomiting and abdominal cramps. Tube feedings were carried out with some success. Vitamins, calcium and analgesics were given. On the seventeenth hospital day, the patient complained of increasingly severe abdominal pain and increased vomiting. On the eighteenth hospital day she went into shock and expired.

Post-mortem studies showed an emaciated body. The abdomen was markedly distended. There was 1000 ml. of clear sero-sanguinous fluid in the abdomen. There was a huge, dilated, dark-red, redundant loop of bowel which arose from the left lower quadrant and extended to the right upper quadrant. This loop represented a volvulus of the sigmoid. The small intestine was moderately dilated and pale. The stomach was not dilated. The heart weighed 190 gm. There was evidence of old healed mitral valvulitis. The lungs together weighed 650 gm. and were grossly normal. The liver weighed 1370 gm. It was very flabby with a smooth surface and rounded edge. The spleen weighed 45 gm. Grossly and microscopically, the organ was normal. The adrenals were normal grossly. The pancreas was normal. The kidneys revealed old pyelonephritic scarring. The esophagus was normal. The stomach was not dilated. The mucosa was thin and the rugae flattened. The jejunum and ileum were dilated and the mucosa was less velvety than usual. Microscopically, there was such autolysis that it was difficult to interpret the sections. However, the mucosa appeared atrophic and the villi broadened. In many of the muscle fibers of the muscularis layer of the small bowel there was a granular pigment which did not stain as iron. The colon to the area of volvulus was moderately dilated. The lumen of the twisted sigmoid was filled with dark old blood and gas. The mesenteric lymph nodes showed fibrous cords in the sinusoids. The bone marrow appeared normal grossly.

Cause of death. Acute intestinal obstruction secondary to volvulus of sigmoid.

Case 9

A 51 year old white female was hospitalized in February 1951 because of weight loss and diarrhea. For the previous 11 years she had had recurring episodes of diarrhea consisting of 10 to 20 bulky, foul-smelling bowel movements daily. Treatment with vitamins and liver extract resulted in improvement. Three months before admission she began having frequent attacks of carpo-pedal spasms. Examination revealed a thin, chronically ill female. The adbomen was distended with visible peristalsis. Trousseau and Chvostek signs were positive. The hemoglobin was 9.5 gm. per cent with a hematocrit of 29 per cent and 2,186,000 RBC. The oral glucose tolerance test was flat. There were large quantities of neutral fat and fatty acids in the stool. X-ray examination of the gastrointestinal tract was not diagnostic. Serum calcium ranged from 5.1 to 7.2 mg. per cent. Bone marrow revealed a megaloerythroblastic picture. Treatment, consisting of calcium, vitamin B_{12} and folic acid, resulted in little or no improvement. She developed several severe crises of abdominal distention, the last one on the twenty-seventh hospital day, was refractory to any therapy. She went into shock and expired.

Post-mortem examination revealed an emaciated body. The abdomen was distended. There was a healed scar of a right radical mastectomy. The small and large bowel were markedly distended by gas and feces. The distention ceased abruptly at the splenic flexure but no obvious cause for this phenomenon was found. There were no adhesions and the serosa was smooth and shiny. There was no fluid in the peritoneal cavity. The heart weighed 175 gm. and was grossly normal. The lungs together weighed 680 gm. There was emphysema as well as focal atelectasis. The spleen weighed only 25 gm. The organs were otherwise normal grossly and microscopically. The liver weighed 1150 gm. and revealed on section the normal architecture and scattered yellowish foci .1 to .3 cm. diameter. There was moderate generalized congestion.

The pancreas was normal grossly. The adrenals likewise appeared normal. The kidneys together weighed 221 gm. There were no gross or microscopic abnormalities. The esophagus was normal. The stomach was moderately dilated by gas and undigested food. The mucosa was slightly flattened. The duodenum was moderately dilated and the mucosa reddened. The remainder of the small intestine was markedly dilated. The mucosa appeared normal grossly. There were scattered bullae of air beneath the mucosa in some areas. The large bowel showed similar features. The marked dilatation extended to the splenic flexure. Microscopically, the mucosa of the small and large intestine was without change. The villi were not clubbed or atrophic. There was no pigmentation of the musculature. The descending colon and rectum were normal. The mesenteric lymph nodes were slightly enlarged; microscopically, there was accentuation of the connective tissue septa. The vertebral bodies showed severe osteoporotic changes. The traveculae were thinned. The bone marrow was grossly normal.

Cause of death. Acute dilatation of the intestine, volvulus?, angulation?.

Case 10

A 67 year old white male was first hospitalized in February 1955 because of diarrhea of eight years' duration. The stool was watery, brown and occasionally accompanied by abdominal cramping. He had lost 12 pounds in the previous year. On examination, he was emaciated and there was some abdominal distention. There was clubbing of the fingers and toes. Examination of the blood revealed: hemoglobin, 13.9 gm. per cent; total protein, 5.4 gm. per cent; albumin, 3.3, and globulin, 2.1 gm. per cent; fasting blood sugar, 75 mg. per cent; calcium, 8.5 mg. per cent; phosphorus, 2.2 mg. per cent; stool fat, 66.4 per cent of dry weight (40 per cent fatty acid and 26 per cent neutral fat). An oral glucose tolerance test was flat. A gastrointestinal roentgen series was interpreted as showing changes most consistent with a granulomatous process involving the stomach, duodenum and jejunum. Gastroscopy was normal. Treatment, consisting of high protein diet and vitamins, resulted in some improvement and the patient was discharged. Diarrhea continued, averaging six movements daily. The patient again began to lose weight. He was readmitted in August 1955 in a state of extreme emaciation. Blood studies were as follows: hemoglobin, 11.8 gm. per cent; WBC, 10,000 per cu. mm.; Ca, 6.8 mg. per cent; P, 3 mg. per cent; K, 1.8 mEq./l.; Na, 148 mEq./l.; chloride, 115 mEq./l. Therapy, consisting of intravenous fluids, electrolytes, intravenous ACTH and albumin, were unavailing and the patient expired on the third hospital day.

Post-mortem examination revealed a badly emaciated body. There was clubbing of the fingers. The abdominal wall was very thin with no panniculus. There was a small amount of serous fluid in the abdominal cavity. The heart weighed 190 gm. The myocardium had a slightly brownish color. There was moderate atherosclerosis of the aorta. The lungs together weighed 1500 gm. On cut section, the lungs were reddened and much clear fluid was expressed. The trachea and bronchi contained frothy fluid. The liver weighed 800 gm. On cut section the lobular architecture was normal. The spleen weighed 82 gm. On cut section the usual architecture was apparent. The pancreas was grossly normal. The adrenals were grossly normal. The kidneys together weighed 222 gm. and were grossly and microscopically normal.

The esophagus was normal in caliber and had a smooth, intact mucosa. Microscopically, there was a mild round cell infiltration of the submucosa The stomach was slightly dilated but its mucosa appeared normal. The duodenal mucosa was brownish-red in color with submucosal hemorrhages and congestion seen microscopically. The jejunal and ileal bowel wall was very thin and the mucosa was atrophic. Microscopically, there was absence of villi and glands with vacuolar degeneration of the musculature. The colon was normal in all respects. The mesenteric nodes were not enlarged. The bone marrow was scanty.

Cause of death. Cachexia.

Case 11

A Canadian-born, white, male, who was 38 years old at the time of his death in 1954, had been well until 1950 when he noted onset of frequent bulky stools, abdominal cramps and weight loss. Six months later, he was hospitalized because of the passage of large quantities of bright red blood by rectum. The cause of the bleeding was not ascertained. Because of the persistence of diarrhea and weight loss he was admitted to The Mount Sinai Hospital for the first time in February 1951. Total fecal fat was 33.5 to 46.1 per cent of dry stool weight. Glucose tolerance and vitamin A tolerance test curves were flat. Gastro-intestinal x-ray series revealed flocculation and segmentation of barium, thickening of mucosal folds and dilatation of many loops of small bowel. Pancreatic secretin studies were normal. A diagnosis of primary sprue was made and the patient was treated with a low-fat diet, parenteral and oral folic acid and vitamin B_{12} with some improvement.

Two months later, he had an unexplained attack of abdominal pain and fever which subsided after a few days of conservative therapy. In June of 1951, because of exacerbation of his diarrhea and weight loss, corticotropin was started. Subsequently, cortisone was substituted for ACTH. He did well on this therapy until July 1953 when he again experienced an attack of abdominal pain thought to be consistent with an intestinal perforation but treated conservatively. In August 1953 he had another episode of intestinal bleeding. In March 1954 he experienced a third attack of severe abdominal pain and fever. With each attack of pain or bleeding, cortisone was temporarily withheld. In April 1954 he experienced another attack of massive gastro-intestinal bleeding for which a subtotal gastrectomy was performed. Cortisone was withheld but reinstituted because of recurrence of diarrhea. An attack of abdominal pain thought to be due to intestinal perforation occurred in July 1954. Two weeks later, bleeding recurred and a revision of the gastrectomy was performed. From this point until his death in September 1954 his course was one of progressive cachexia.

Steroid therapy caused some improvement from time to time but invariably was followed by bleeding or abdominal crises (? perforations).

Post-mortem examination revealed anasarca and emaciation. There was 500 ml. of clear amber fluid in each pleural cavity and 800 ml. of similar fluid in the abdominal cavity. There were numerous fibrinous peritoneal adhesions. A subtotal gastrectomy and gastroenterostomy had been performed. There was a perforation of the jejunum adjacent to a left sub-diaphragmatic abscess cavity. There was a 1 cm. embolus in the right pulmonary artery occluding the middle lobe branch. The middle lobe was infarcted. There was moderate edema throughout the remainder of the lungs. The heart weighed 340 gm. There was an excess of pericardial fluid. The left ventricular wall was slightly hypertrophied. There was a small amount of brown pigmentation scattered throughout the myocardium microscopically. The aorta showed minimal atherosclerotic changes. There were thromboses of both iliac veins. The spleen weighed 230 gm. Microscopically, there was congestion and an increase in plasma cells. The liver weighed 2400 gm., was extremely friable and had a greasy appearance. There was marked centrilobular congestion. There was a heavy cellular infiltrate consisting mainly of polymorphonuclear leucocytes in the periportal area. The pancreas weighed 80 gm. and was normal grossly and microscopically. The adrenal cortex was exceedingly thin and almost white in color. The layers of the cortex were not well defined microscopically. The zona fasciculata was particularly indistinct. There was moderate congestion. The esophagus was normal. The remaining gastric pouch had an extremely thin and friable wall. The mucosa was somewhat atrophic. There was marked post-mortem autolytic change in the stomach. The wall of the small intestine and proximal half of the colon was extremely thin and friable. Throughout the duodenum, jejunum and proximal ileum there were numerous shallow ulcerations in the mucosa measuring 0.5 to 3.0 cm. These ulcers were extemely ragged with many having a necrotic zone and raised edges.

The majority of the lesions, however, were simply irregular defects in the mucosa without secondary defects in the mucosa and without secondary inflammatory change. One of the jejunal ulcerations had perforated at the site of the abscess cavity. There were several areas throughout the jejunum where the bowel wall was thick and reddened for distances up to 15 cm. The gross appearance of these areas suggested jejunitis. The mucosa of the colon showed no evidence of ulceration or erosion. The mesenteric lymph nodes measured 0.3 to 1.5 cm. and were moderately firm and dark brown. The mesentery was slightly thickened and revealed many yellow streaks running from the bowel toward the root. Microscopically, the small bowel revealed flattening of the mucosa and extensive autolytic change. In some areas, there was an increase in the cellular composition of the sub-mucosa. The ulcer beds contained a moderate number of polymorphonuclear leucocytes. In some areas, there was an eosinophilic smudging of the arterial walls. In the thickened areas of jejunum, there was thickening, fragmentation and fibrinoid change of the musculature. There was a moderate diffuse cellular reaction consisting of macrophages, lymphocytes and a few segmented lymphocytes. Autolytic change in the colon was extensive. Many of the mesenteric vessels and lymphatic capillaries were surrounded by small collection of round cells. There was a small amount of fibrinoid material surrounding many of the lymphatic vessels. The mesenteric lymph nodes were almost completely replaced by a large amount of fibrinoid and fibrous material. A few small follicles remained. Examination of the urinary tract revealed a mild focal pyelonephritis. The pituitary was normal.

Cause of death. Cachexia, gastrointestinal bleeding, pulmonary infarction.

POST-MORTEM FINDINGS IN IDIOPATHIC SPRUE

In the eleven cases presented above, the cause of death was directly or indirectly related to the sprue syndrome. All but three of the patients died during a period of relapse. Of those in remission at the time of death, one died following appendectomy for acute appendicitis (Case 1), another of acute yellow atrophy (Case 3) and a third of necrotizing tracheo-bronchitis (Case 6). Of the eight pa-

TABLE I

Summary of findings at autopsy

Case	Stomach	Small Intestine	Large Intestine	Mesenteric Lymph Nodes	Pancreas	Liver	Spleen	Bone Marrow	Adrenals	Parathyroid	Skin	Comment
1	Gross: atrophy Micro.: atrophy	Normal No info.	Normal Normal	Normal No info.	Normal Normal	1,920 gm. Centrolobular fibrosis; fat moderate	490 gm. Hyperemia; fibrosis; "acute splenitis"	Spongy, red Erythroid hyperplasia	Normal Normal	No info.	No info.	Cause of death: appendicitis
2	Gross: flat, pale Micro.: within normal limits	Congestion Marked hemofuscinosis of muscularis propria	Congestion Mild hemofuscinosis	Enlarged Within normal limits	Normal Interlobular fibrosis, moderate	1,240 gm. Congestion	150 gm. (enlarged) Hyperemia; lining endothelial hyperplasia	Spongy, red Decided erythroid hyperplasia	Normal Normal	Normal Normal	Normal Iron free pigmentation, basal layer	Cause of death: multiple hemorrhages Deformed dwarf
3	Gross: normal	Normal, "velvety mucosa"	Normal	Enlarged	Normal	1,100 gm.	210 gm.	Spongy, red	Normal	Normal	Pigmentation; follicular hyperkeratosis	Cause of death: liver necrosis and multiple hemorrhages
	Micro.: slight atrophy of pyloric mucosa	Villous clubbing with hyaline villous bans	Much mucus	Chronic lymphadenitis	Some acinar atrophy	"Acute yellow atrophy"	"Acute splenitis"	Increased fat, paucity of megakaryocytes; erythroid activity good	Normal	Congestion and hemorrhages	Melanin	
4	Gross: atrophy	Normal	Normal	Normal	Enlarged	2,080 gm.	75 gm.	Normal	Normal	Normal	Normal	Cause of death: marantic thrombosis of dural sinus and cerebral veins
	Micro.: autolysis, small myoma	Normal except for 2 serosal chondromas and some fibrous adhesions	Normal	Normal	Fine fibrosis	Extreme steatosis	Fibrosis; hemosiderosis	Increased fat with pronounced erythroid activity	Normal	Conspicuous connective tissue proliferation	—	General atrophy of viscera except liver and pancreas
5	Gross: massive dilatation	Massive dilatation; brownish pigmentation of the muscularis	Normal except for brownish pigmentation of the muscularis	Enlarged	Normal	1,875 gm.	190 gm.	Spongy, red	Autolysis	Normal	Pigmentation	Cause of death: volvulus of the sigmoid with resection, and acute purulent pyelonephritis
	Micro.: hemofuscin in muscle	Hemofuscinosis of the muscularis propria atrophy of the muscularis	Hemofuscinosis of the muscularis propria	Unusual, disproportionate trabeculation	Severe interlobular and intralobular fibrosis	Congestion	"Acute splenitis"	Active myeloid and erythroid series	Autolysis	—	Melanin; hemosiderosis, slight	Hemofuscinosis; old "neurodermatitis" and brawny edema of the legs

6	Gross: normal	Normal	Normal	Enlarged	Normal	1,580 gm.	300 gm.	Spongy, red	Normal	Normal	Normal	Cause of death: acute necrotizing laryngotracheitis (influenza virus B)
	Micro.: normal	Increased leukocytes in lamina propria: occasional bizarre villous shapes	Endometriosis, focal	Unusual, disproportionate trabeculation	Intralobular fibrosis	Normal	Fibrosis and "acute splenitis"	Increased fat; increased erythroid activity	Autolysis	Normal	—	Status 1 yr. after drainage of left subphrenic abscess
7	Gross: dilated; mucosa atrophic	Duodenum markedly dilated; superficial necrosis	Atrophic	Enlarged	Fibrotic	Normal	Normal	No. info.	Normal	No. info.	No. info.	Cause of death: broncho-pneumonia, emaciation.
	Micro: mucosa atrophic	Superficial necrosis of duodenum and ileum	Atrophic	Hyperplastic lymphadenitis	No info.	Fatty degeneration	Acute splenitis	No. info.	No. info.	No. info.	No. info.	
8	Gross: mucosa flattened	Dilated	Volvulus of sigmoid; proximal colon dilated	No info.	Normal	1370 gm.	45 gm.	Normal	Normal	No. info.	No. info.	Cause of death: acute intestinal obstruction secondary to volvulus of sigmoid
	Micro: no info.	Autolysis	No info.	Fibrous cords in sinusoids	No info.	Normal	Normal	No info.	No info.	No info.	No info.	
9	Gross: dilated; mucosa atrophic	Markedly dilated jejunum and ileum	Dilated proximal to splenic flexure	Normal	Normal	1150 gm.	25 gm.	Normal	Normal	No info.	No. info.	Cause of death: dilatation of intestine ? volvulus ? angulation
	Micro: no info.	Normal	Normal	Accentuation of tissue system	No info.	Fatty change	Normal	No info.	No info.	No info.	No info	
10	Gross: slightly dilated	Thin wall, atrophy of mucosa	Normal	Normal	Normal	800 gm.	82 gm.	Scanty	Normal	No info.	No info.	Cause of death: cachexia
	Micro: no info.	Absence of villi and glands; vacuolar degeneration of musculature	Normal	No info.	No info.	Normal	Normal	No info.	No info.	No info.	No info.	
11	Gross: thin wall; atrophy	Thin wall; ulcerations of small bowel; perforation of jejunum	Thin wall of descending and proximal transverse colon	Enlarged	80 gm.	2400 gm. friable	230 gm.	No info.	Cortex extremely thin	No info.	No info.	Cause of death: cachexia, gastrointestinal bleeding, pulmonary infarction
	Micro: autolytic change	Atrophy, ulceration, cellular infiltration	Autolytic changes	Fibrinoid and fibrous tissue replacement	Normal	Congestion; heavy cellular infiltrate in periportal areas	Congestion	No info.	Congestion	No info.	No info.	

tients who were in clinical relapse at the time of their death one died of severe hemorrhagic manifestations and tetany (Case 2); one succumbed to volvulus of the sigmoid (Case 8); another to acute pyelonephritis following resection of the sigmoid for volvulus (Case 5); one died of ileus probably caused by angulation or volvulus of the splenic flexure; four patients died of extensive cachexia complicated in three by such conditions as marantic thrombosis of the dural sinus and cerebral veins (Case 4), confluent bronchopneumonia (Case 7), and gastrointestinal bleeding associated with prolonged steroid therapy (Case 11). The following is a summary of the findings in the organs (Table I).

Stomach. In seven of the cases the gastric mucosa was found to be grossly atrophic. This change was described on microscopic examination in four instances. In two patients extensive autolytic change prevented adequate description. Gross dilatation of the stomach was found in four instances. In Case 5, hemofuscinosis of the cytoplasm of the smooth muscle cells was present. In one patient there were numerous plasma cells and leukocytes in the lamina propria.

Small Intestine. In four instances the small intestine was found to be grossly normal. In two of these cases, microscopic examination was also normal. Atrophy and thinning of the wall was the outstanding change in the others (Fig. 1A). Gross dilation was described in three instances, two of which were associated with intestinal obstruction due to volvulus. Changes of the villi, consisting of flattening and thickening of the tips (clubbing), were specifically described in four cases (Fig. 1B, C). In other instances this change was apparently obscured or confused with post-mortem autolytic change. Moderate increase in the cellularity was frequently found. In one patient (originally described by Schein (5)) peculiar stromal hyaline band formations associated with marked deformation of the villi were found in all parts of the small intestine. In two cases large amounts of granular pigment, probably hemofuscin, were found in the muscularis (Fig. 2).

Large Intestine. The colon in the majority of instances was normal. The mucosa did not reveal the atrophic features found in the small bowel except in one case. Two of the patients died as a result of volvulus of the sigmoid. A third patient was believed to have died as the consequence of either a volvulus or an angulation of the splenic flexure. The marked dilatation of the colon in these patients might have been a predisposing factor in the development of the volvulus (15). An additional predisposing factor may have been the presence of a long mesentery. Minimal hemofuscinosis of the muscularis of the colon was seen in two instances.

Mesenteric Lymph Nodes. The mesenteric lymph nodes were enlarged in five cases. Many of these nodes revealed an unusual, disproportionate fibrous trabeculation. In three cases there was a chronic lymphadenitis. In Case 11 the lymphatic capillaries were markedly dilated and were surrounded by chronic inflammatory cells as well as an unusual variety of large cells resembling mast cells (Fig. 3).

Pancreas. The pancreas revealed various degrees of intralobular and interlobular fibrosis in four cases. These changes for the most part were not marked. In the remaining cases, the pancreas was grossly and microscopically normal.

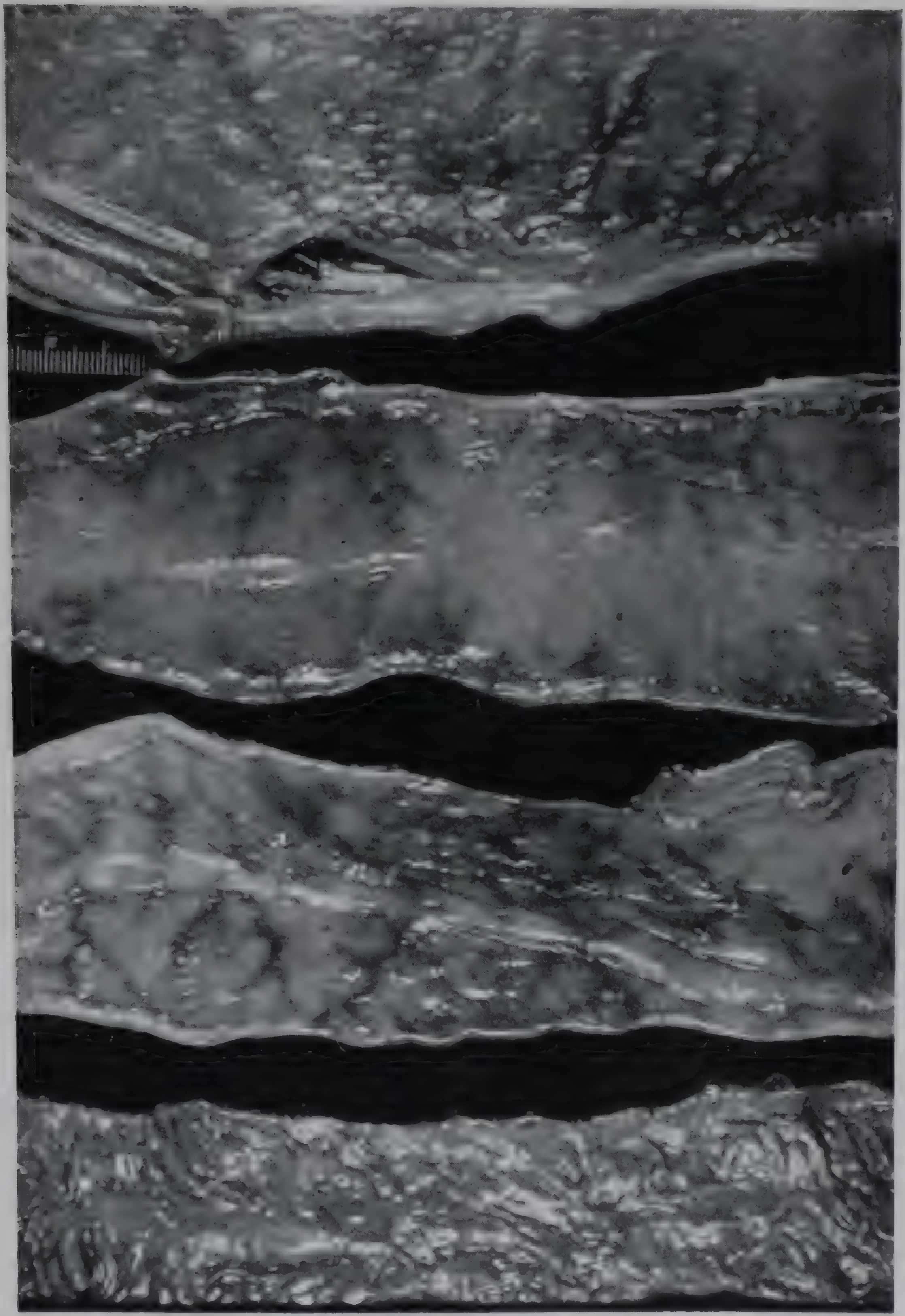


FIG. 1A. Diffuse atrophy and thinning of small bowel wall (Case 10, autopsy material).

There was no evidence of biliary disease. Some acinar atrophy as seen in hunger states was found in one case.

Liver. The liver varied in weight from 800 to 2400 gm. Several of the cases showed hepatomegaly of various degrees. Fatty changes, especially marked in Case 4, were seen in several instances, whereas others merely showed congestion. There was no uniform or characteristic appearance of the liver. In Case 3, an unexpected and severe acute yellow atrophy was found at autopsy examination. One case revealed centrilobular fibrosis. In Case 11, the liver was extremely

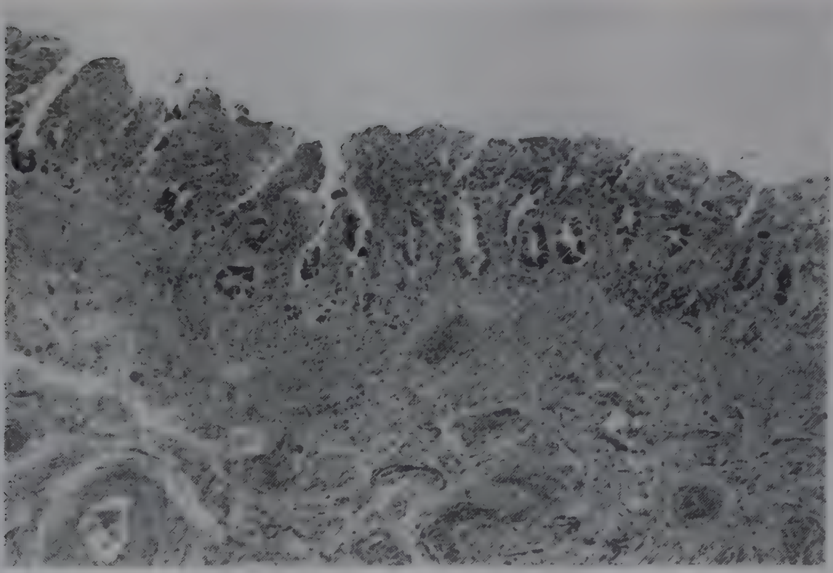


Fig. B

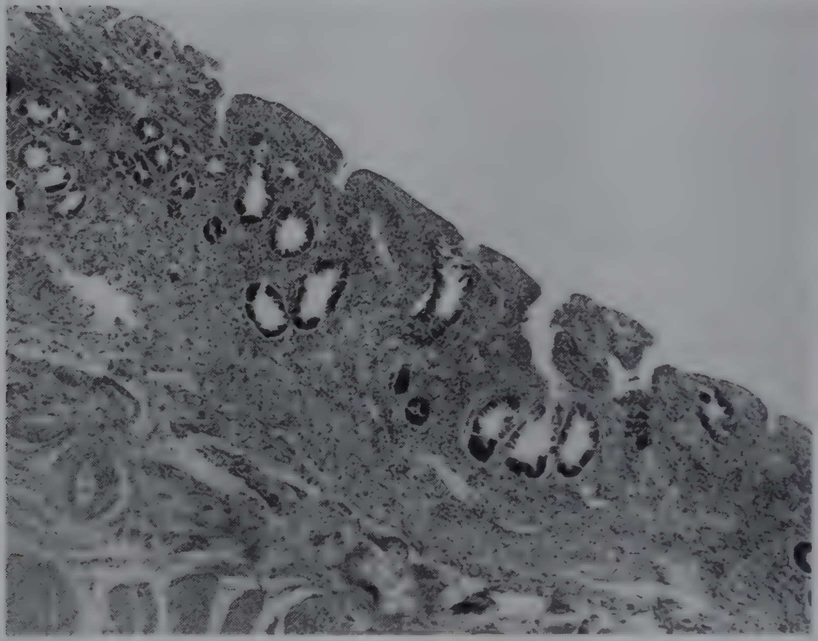


Fig. C

Fig. 1B & C. Flattening and thickening (clubbing) of villi as seen in autopsy cases.

friable and there was a heavy periportal leukocytic infiltration probably related to the patient's septic state.

Spleen. The spleen varied in weight from 45 to 410 gm. Five of the cases showed an acute "splenitis". There were varying degrees of congestion in several instances. Three cases revealed an unusual degree of fibrosis.

Bone Marrow. The bone marrow in four cases revealed erythroid hyperplasia associated with an otherwise hypoplastic marrow with increased amounts of fat.

Adrenals. The adrenals revealed no abnormal change except in Case 11, in which the cortex was unusually thin. This was the only patient of this series who had received prolonged steroid therapy.

Parathyroids. In the five cases in which the parathyroids were described, in only one instance was there any abnormality. In Case 4 there was a conspicuous connective tissue proliferation throughout the gland. Evidence of parathyroid hypertrophy was not seen.

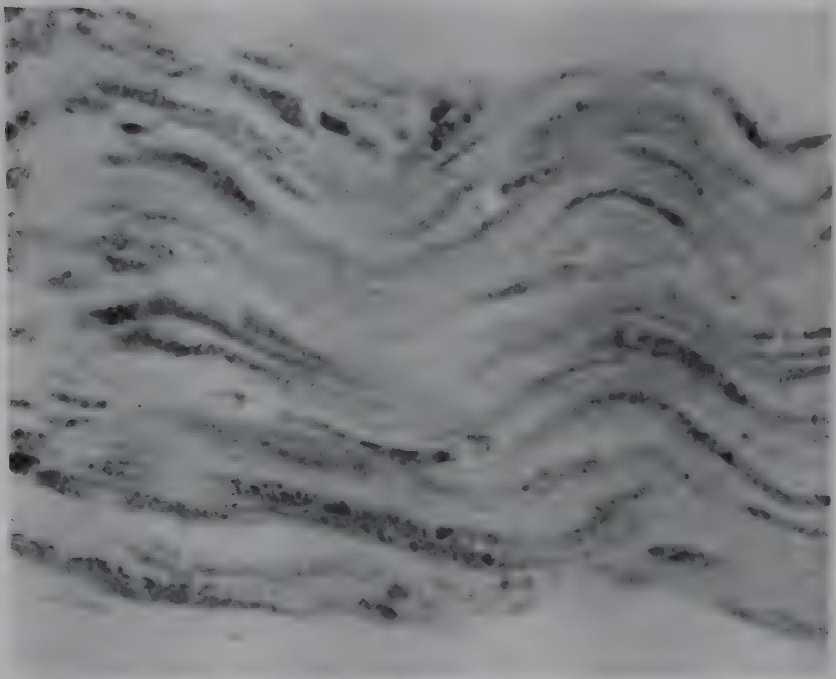


FIG. 2. Granular pigment in the muscularis (autopsy material).

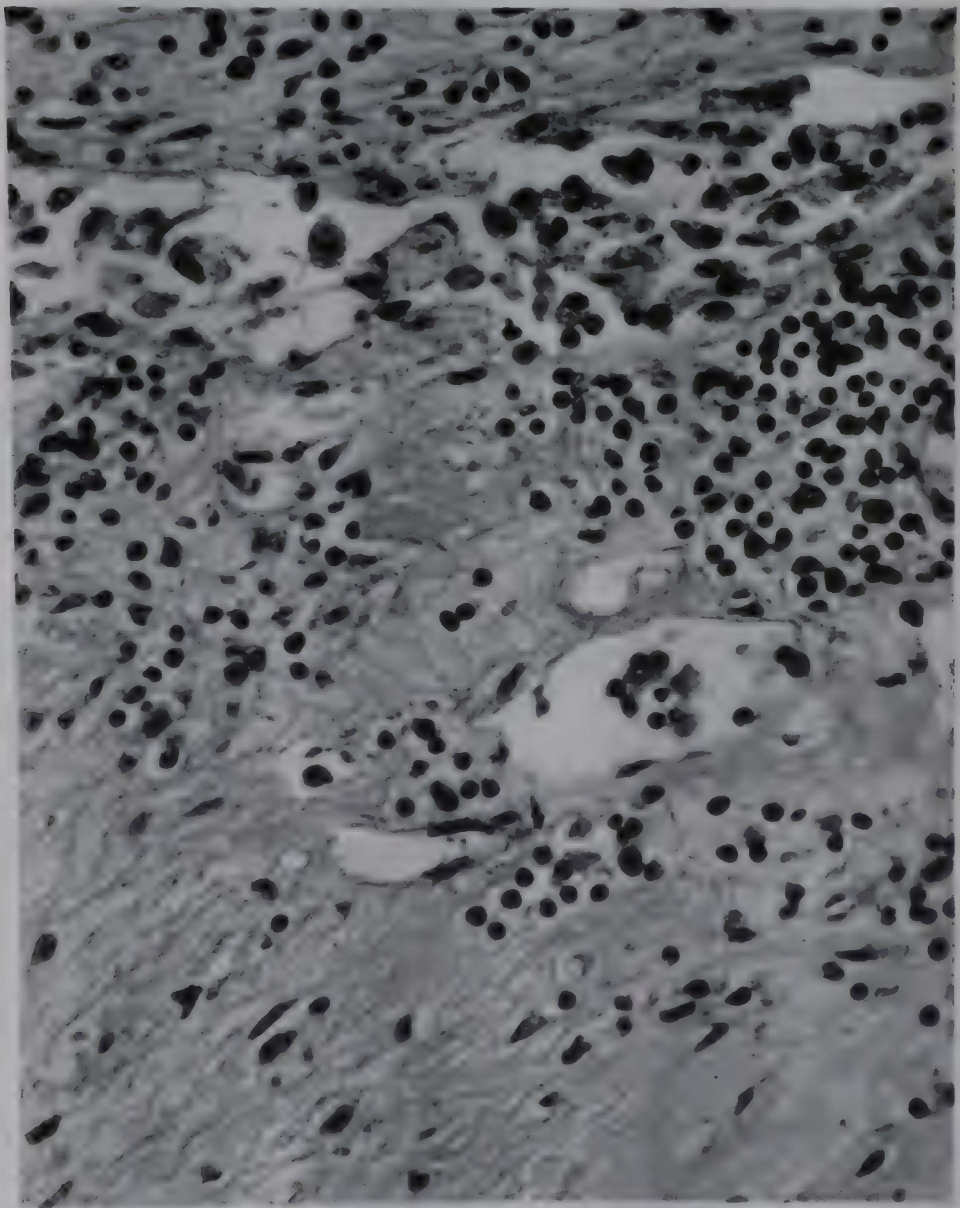


FIG. 3. Mesenteric lymph node (Case 11, autopsy material). Note dilatation of lymphatic capillaries surrounded by chronic inflammatory cells and replacement of lymphoid by fibrous tissue.

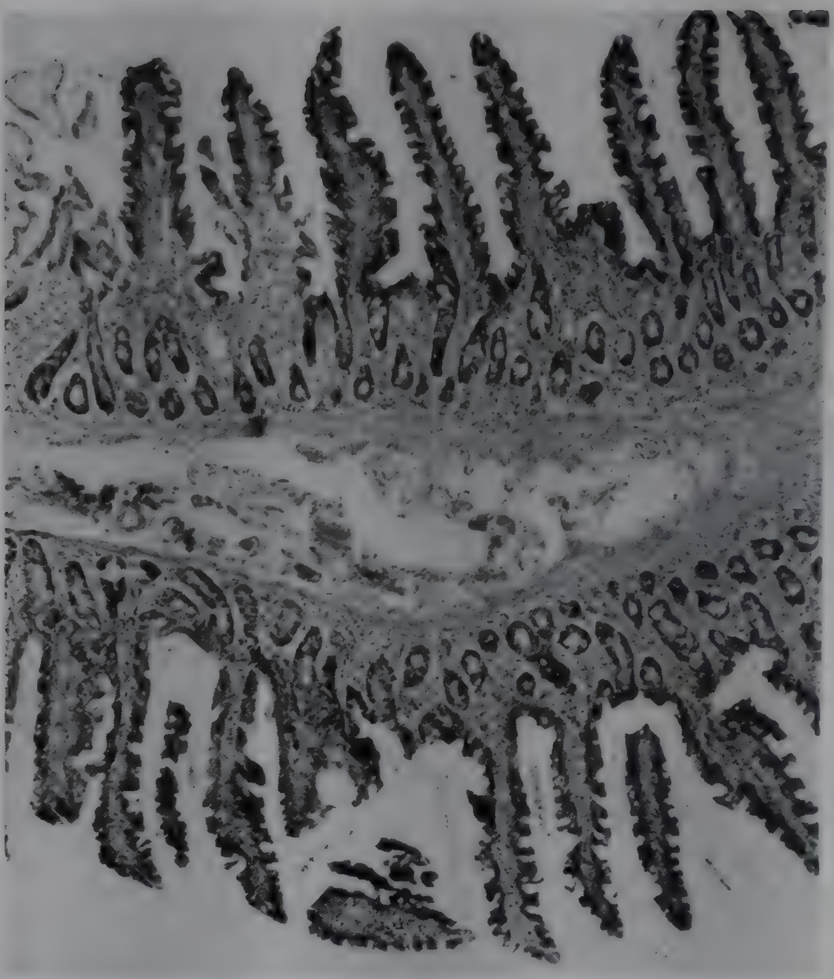


FIG. 4. Finger-like appearance of normal villi (Jejunal biopsy).

Skin. The skin was examined in five cases, three of which showed various degrees of pigmentation. There was an increase of iron-free pigmentation (melanin) in the basal layer.

STUDIES OF BIOPSY MATERIAL

Jejunal biopsies were performed in four patients with sprue, currently undergoing treatment with corticosteroids, by Dr. M. Shiner utilizing her modification of the Wood biopsy instrument (13). In addition, two patients, of whom one had clinical malabsorption other than sprue (pancreatic insufficiency secondary to carcinoma), and the other pernicious anemia, were studied. In the latter two cases the jejunal mucosa was normal. In the sprue patients the changes were striking. The villi, instead of having the normal narrow finger-like configuration (Fig. 4), were markedly thickened and flattened, with considerable loss of villous surface area (Fig. 5). The surface epithelium covering the villi assumed a cuboidal shape rather than the usual columnar type of epithelium. The striated border, however, was well preserved. The nuclei were irregular in shape and position within the cells. There appeared to be an increase in the number of goblet cells. In the lamina propria there was slightly more than the average cellular infiltration consisting mainly of lymphocytes, plasma cells and occasionally eosinophils.

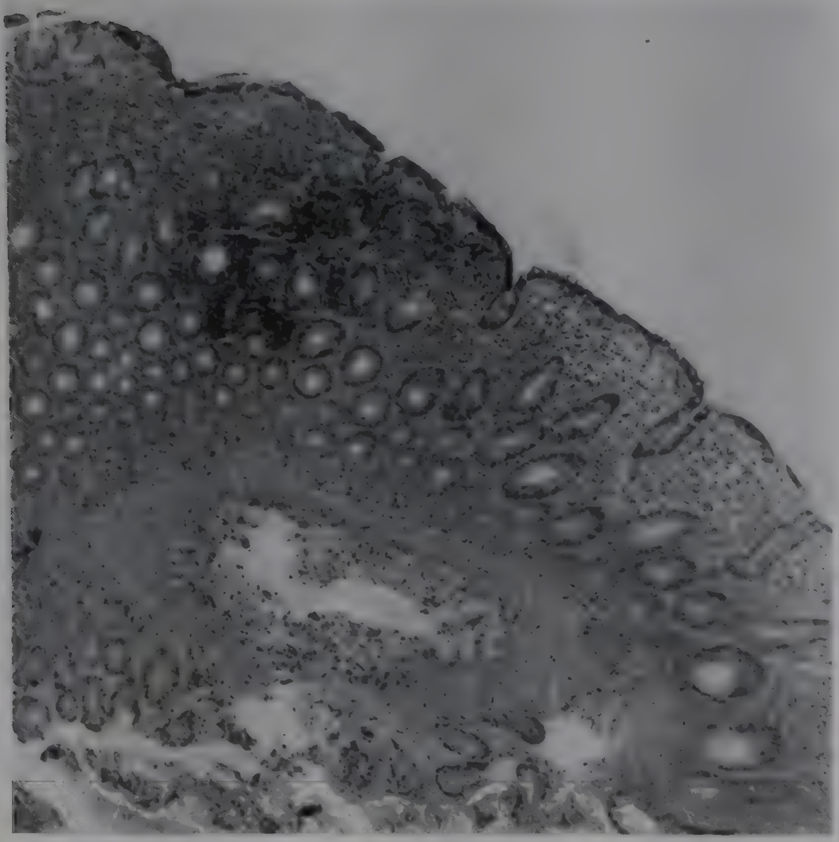


FIG. 5. Marked thickening and flattening of villi with considerable loss of absorbing surface area (Jejunal biopsy). Patient received prolonged steroid therapy.

A more detailed analysis of the biopsy findings is presented elsewhere in this symposium (14).

DISCUSSION

In the post-mortem examinations no characteristic or uniform pattern of pathological aberration is apparent. The logical assumption, based on clinical evidence that the malabsorption syndrome in sprue is due to a derangement or defect in the small bowel, is not conclusively supported by evidence obtained from autopsy material. Since a number of the autopsied cases and all of the biopsied cases revealed some change in small bowel morphology, it would appear that this change is causally related to the clinical picture. The marked atrophy of the small intestinal mucosa and the blunting and thickening of the villi seen in many of the cases obviously lessen the surface area available for absorption. It might of course be argued that those changes in the mucosa are the result of alterations in small bowel motility, stasis, changes in intestinal flora, absorption of toxic products or lack of specific nutritional factors, such as are seen in pernicious anemia where gastric mucosal atrophy is believed to result from a prolonged deficit of vitamin B_{12}-intrinsic factor. In many instances, post-mortem autolytic change has been so extensive as to prevent interpretation of the findings. The large bowel does not appear to participate in this process to any great extent.

It would appear that study of material obtained by jejunal biopsies in living patients would permit a more exact interpretation of any pathological change by eliminating the factors of agonal and post-mortem autolysis seen in many autopsied cases. The normal mucosa obtained by the oral biopsy technique reveals thin finger-like villi. The jejunal villi of sprue patients are thick and blunt. The area available for absorption from the lumen is markedly diminished. The degenerative changes seen in the surface epithelium may likewise contribute to the absorption defect. The apparent increase in the goblet cells suggests hypersecretion of mucus, possibly as a response to irritation. It is significant that one patient who had pancreatic insufficiency secondary to carcinoma and was markedly cachectic had a normal jejunal mucosa. The oral technique of obtaining biopsy material is a significant contribution to the study of small intestinal disease.

The significance of pigmentation observed in the small intestine in some of the cases is not clear. Pappenheim and Victor (16) have described the presence of "ceroid" pigment in animals deficient in vitamin E and in man with malabsorption syndrome. In the latter category it is believed that vitamin E deficiency is part of the overall deficiency of fat-soluble vitamins (vitamin A, chemical and clinical evidence; vitamin K, hypoprothrombinemia; vitamin D, abnormalities of calcium metabolism).

It is not clear what the changes in the mesenteric lymph nodes signify. Are the evidences of chronic lymphadenitis and fibrosis primary, producing blockage of the lymphatic channels and hence diminished absorption? In only one instance was there evidence, in the form of distended mesenteric lymphatic capillaries, that this explanation is feasible. It is more likely that the changes are secondary to a chronic degenerative process in the bowel.

Interpretation of the significance of the varying degrees of fibrosis of the pancreas is obscure. It is perhaps related to the severe nutritional deficiency (17). Because this change was not observed in many of the cases, there probably is no pathogenetic significance which can be ascribed to these findings.

Similar conclusions may be drawn for the role of the liver in sprue. The most consistent, but not invariable, finding was some degree of fatty change resulting probably from the nutritional defects in these patients. Similarly, the instance of acute yellow atrophy probably represents an unusual complication in a malnourished individual. Sepsis and malnutrition may prove responsible for friability and increased cellular infiltration observed in Case 11.

There were no changes in the spleen considered to be of significance.

Although both the adrenal (18) and parathyroid (19) glands have been reported as being implicated in the cause of sprue, there was no evidence in the present study to substantiate these contentions. Atrophy of the adrenals, noted in Case 11, was believed to have been secondary to the prolonged use of steroid hormones. The connective tissue proliferation of the parathyroids noted in Case 4 cannot be explained. In no instance was there evidence of hyperparathyroidism as might be expected in patients with long standing steatorrhea.

Erythroid hyperplasia of the bone marrow, which was present in several cases, is a non-specific finding frequently seen in anemic states. The absence of megaloblastic patterns at autopsy is due to preceding therapy with liver extract and/or vitamin B_{12}. The previously described changes in osteomalacia could not be confirmed since no osseous tissue was removed for examination in any of the cases.

The skin pigmentation in the few cases in which it was described was due to an increase in the melanin content in the basal layers. Hemofuscin has not been found in any case.

It may be concluded from these studies that the major and significant pathologic aberrations are to be found in the small intestine. Although it is conceivable that the absorptive defect may result solely from these physical and morphological changes, it is also possible that the changes are secondary to some other defect which results in mucosal atrophy, much as prolonged vitamin B_{12}-intrinsic factor insufficiency results in gastric atrophy in patients with pernicious anemia (20).

It is conceivable that the basic defect of absorption in sprue is caused by an alteration in genetically controlled enzymatic mechanisms in the intestinal mucosa and that morphologic changes are secondary to this disturbance. Studies of enzymatic activity of small intestinal mucosa obtained by biopsy would undoubtedly be fruitful. Similar studies evaluating the role of steroid hormones would likewise be of great value in the study of this baffling disorder.

SUMMARY

Eleven post-mortem examinations on patients with idiopathic sprue were performed. In addition, jejunal mucosal biopsies were done in four living sprue patients. In all patients in the latter category and in many of the autopsied cases there was marked atrophy of the small intestinal mucosa with morphological changes in the villi which appreciably diminished the area available for absorption. No other organ system appeared to be involved to the extent that it might be considered to play a primary role in this disorder.

It is concluded that the major pathological alterations in sprue are to be found in the small intestine. It is not clear however whether these changes are due to a specific local enzymatic or nutritional defect or whether they result from toxic degeneration or other influences. The use of the small intestinal biopsy technique is considered to be a useful method of studying intestinal malabsorption. It would be especially valuable in the evaluation of milder disturbances of absorption in children and adults.

REFERENCES

1. Adlersberg, D.: Problems of Management of Idiopathic Sprue. N. Y. Journal Med., 55: 3575, 1955.
2. Gee, S.: On the Celiac Affection. St. Bart's Hosp. Rep. 24, 17, 1888.
3. Thaysen, T. E. H.: Non-tropical Sprue. Levin and Munksgaard. London 1932.
4. Adlersberg, D., and Schein, J.: Clinical and Pathological Studies in Sprue. J.A.M.A., 134: 1459, 1947.
5. Schein, J.: Syndrome of Non-tropical Sprue with hitherto Undescribed Lesions of the Intestine. Gastroenterology, 8: 438, 1947.
6. Oehler, V.: Anatomicropathologic Studies on Tropical and Symptomatic Sprue, 7 cases. Gastroenterologia, 79: 257, 1953.

7. Svartz, N., Nyman, E., and Ernberg, T.: Two Cases of Sprue with Advanced Lesions in the Small Intestine. Acta psychiat. et neurol., suppl. 46, p. 307, 1947.
8. Nyman, E.: Ulcerous Jejuno-ileitis with Symptomatic Sprue. Acta med. Scandinav., 134: 275, 1949.
9. Šarić, S.: Symptomatic Sprue due to Nonspecific Jejunitis and Mesenteric Lymphadenitis. Gastroenterologia, 80: 283, 1954.
10. Milanes, F., Leon, R., and Causa, A.: Jejunal Histopathologic Studies through Surgical Biopsy in a Case of Tropical Sprue in Relapse. Rev. Gastroenterol., 18: 182, 1951.
11. Paulley, J. W.: Observation on the Etiology of Idiopathic Steatorrhea; Jejunal and Lymph Node Biopsies. Brit. Med. J., 2: 1318, 1954.
12. Butterworth, C. E.: Paper Presented before the American Gastroenterological Assn., Atlantic City, May 1956.
13. Shiner, M., and Doniach, I.: A Study of X-ray Negative Dyspepsia with Reference to Histologic Changes in the Gastric Mucosa. Gastroenterology, 32: 313 1957
14. Shiner, M.: Small Intestinal Biopsies by the Oral Route—Histopathological Changes in the Malabsorption Syndrome. This volume, page 99.
15. Glazer, I., and Adlersberg, D.: Volvulus of the Colon: A Complication of Sprue. Gastroenterology, 24: 159, 1953.
16. Pappenheimer, A. M., and Victor, J.: "Ceroid" Pigment in Human Tissues. Am. J. Path., 22: 395, 1946.
17. Dreiling, D.: The Pancreatic Secretion in the Malabsorption Syndrome and in Related Malnutrition States. This volume, page 69.
18. Verzar, F., and Laszt, L.: Nebennierenrinde und Fettresorption Biochem. Ztschr., 278: 396, 1935.
19. Scott, H. H.: A New Theory as to the Causation of Sprue. Tr. Roy. Soc. Trop. Med., 8: 16, 1923.
20. Stevenson, T. D., Little, J. A., and Langley, L.: Pernicious Anemia in Childhood. New Eng. J. Med., 225: 1219, 1956.

SMALL INTESTINAL BIOPSIES BY THE ORAL ROUTE

HISTOPATHOLOGIC CHANGES IN THE MALABSORPTION SYNDROME

MARGOT SHINER, L.R.C.P., M.R.C.S., D.C.H.

The method of taking duodenal and jejunal biopsies by the blind suction technique can be used in out-patients as well as in-patients. It requires no special preparation.

INSTRUMENT AND TECHNIQUE

The small intestinal biopsy tube (Fig. 1) is a flexible plastic tube 161.5 cm. long and 5 mm. in diameter. The headpiece is 2.5 cm. long and has a diameter of 1.3 cm. at its widest point. The diameter of the biopsy hole is 3.5 mm. The knife cylinder is 9 mm. long and is riged at the distal end. An airhole is situated in one of its ridges extending down the side of the knife cylinder, thus allowing air to reach the rubber balloon at the distal end of the headpiece. The tailpiece of the instrument contains the other end of the wire which runs along the whole length of the tube to be screwed into the knife cylinder. Attached to the tailpiece is a lateral exhaust to which a manometer and syringe can be attached to provide negative pressure of known amount.

The fasting patient gargles with 2 to 3 ml. of a 1 per cent amethocaine (pontocaine) solution. He is placed on a fluoroscopic screening couch and, lying on his left side, the headpiece of the tube is gently guided to the back of the throat by the operator's two fingers. The patient is asked to swallow and the tube is easily pushed down. Once the stomach is reached, the progress of the headpiece is controlled by fluoroscopy. It is also aided by exerting pressure on the patient's abdomen to swing the headend of the instrument towards the pylorus (Fig. 2). An upright fluorescent screen may also be used, although manual palpation on the patient's abdomen is then somewhat less effective. The patient is then turned on to his right side and instructed to push the tube gently and very slowly into his mouth. Screening is resumed from time to time to watch the progress of the tube. As a rule the balloon is inflated when the headpiece has reached the duodenum, but sometimes the headpiece may pass the pylorus more easily if the balloon is blown up in the stomach. Sterile saline is the most effective way of inflating the balloon. The amount necessary to distend it should be established before introducing the tube. This quantity of saline is then injected through the lateral exhaust with a syringe. When the first or second part of the duodenum is reached (Fig. 3), duodenal biopsy may be taken. The headpiece of the biopsy tube can be carried further into the jejunum up to 20 cm. from the ligament of Treitz (Fig. 4). Owing to limitation in time and facilities of screening no distal parts of the jejunum were entered. But this should be possible in the future and, at least in certain patients, biopsies of distal parts of the jejunum should become available. The shortest time in which the duodenum or jejunum was reached was just under one hour. The average time was 1½ to 2 hours.

Before biopsy is taken the balloon must be deflated using the syringe at the tail-piece. The manometer is then attached between the lateral exhaust tube and the syringe. The opening of the aperture of the headpiece is achieved by a downward movement of the rod of the tailpiece. Once a slight resistance is felt to downward movement of the rod, the rod is arrested, because further pressure will only result in coiling of the wire inside the flexible tube. Suction is then applied to the syringe to produce a negative pressure of 3 to 5 inches Hg on the manometer. It is dangerous to exceed a pressure of 10 inches Hg. Negative pressure is maintained while the tailpiece rod is pulled upwards by a sharp movement closing the aperture and securing the specimen which consists of a superficial piece of the mucosa

---

From the Gastroenterological Department, Central Middlesex Hospital, London and The Department of Medicine, The Mount Sinai Hospital, New York City.

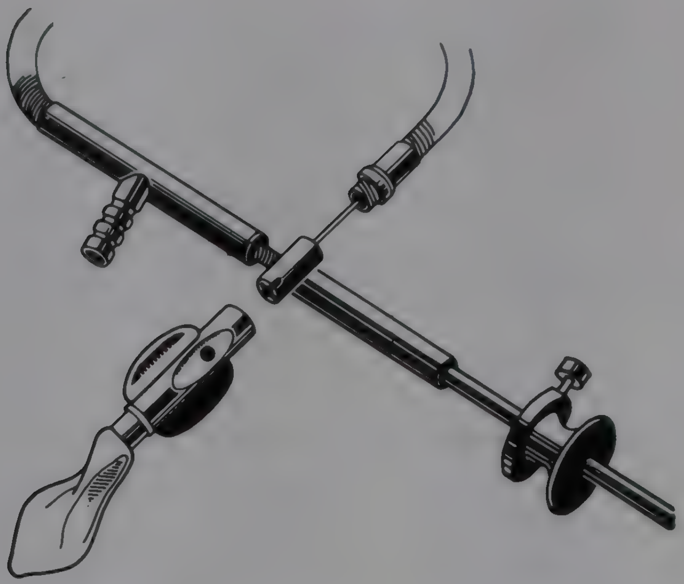


Fig. 1: The jejunal biopsy tube.

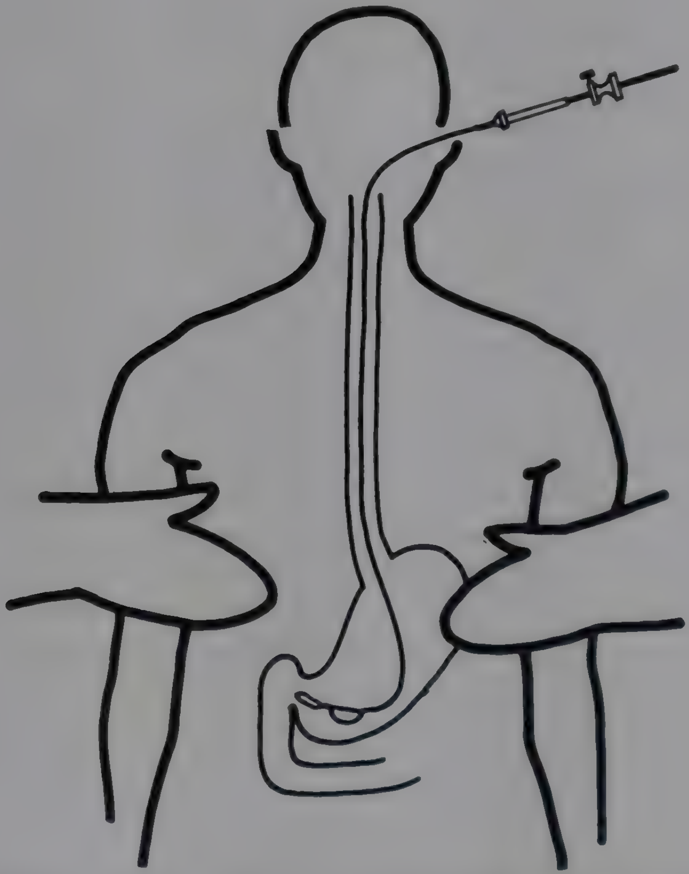


Fig. 2: Tube in stomach with operator's hands on patient's abdomen.

within the headpiece. The syringe is disconnected, air is released and the manoeuver may be repeated. A sort of cutting sensation is transmitted to the operator's hand during the closure of the aperture. To withdraw the tube the patient is turned on his left side, avoiding pressure or traction on the tube during the upward pull. One or more specimens are usually found in the knife blade, or in the flexible part of the tube. These should be blown out gently with the syringe and immediately placed in a 10 to 15 per cent solution of formol in saline and two hours later in formol-saline sublimate for a further 24 hours. The usual histologic procedures are employed. It is important to fix the specimens as soon as possible to prevent autolysis. The patient is instructed to rest for two hours after the procedure. Any food is then allowed.

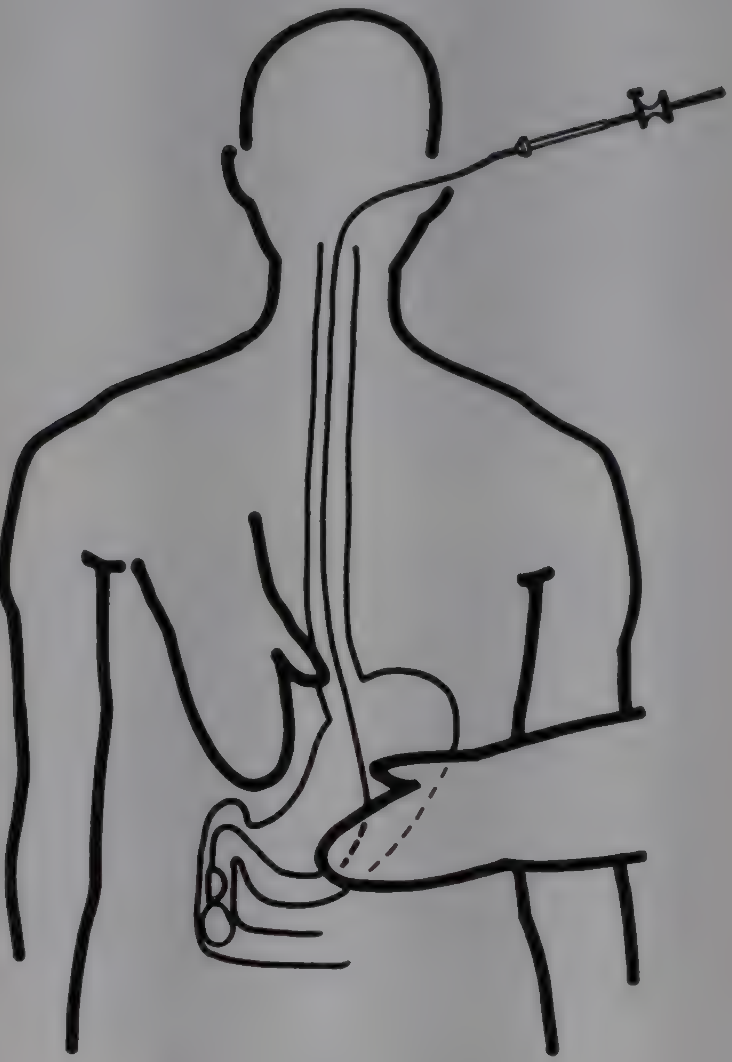


FIG. 3: Tube in duodenum.

Up to date 89 successful small intestinal biopsies have been taken without a single complication. The method may be therefore considered safe, providing reasonable care is exercised. The failure rate is estimated at roughly 1 in 4 biopsies. Failure is due to: 1) Inability to introduce the headpiece beyond the hypopharynx. This is rare; 2) Inability to pass the instrument beyond the pylorus. This still remains one of the most troublesome difficulties encountered; 3) Autolysis of the specimen. This is likely to follow too long a delay in withdrawing the tube, especially in the presence of plentiful intestinal juice inside the biopsy tube.

HISTOLOGIC FINDINGS IN CONTROLS

The specimens obtained varied both in number and size. From one to eight specimens were taken from a single patient. These had a length of 1 mm. to 1 cm., with an average of 3 to 4 mm., and included full thickness mucosa, muscularis mucosae and a thin layer of submucosa. Excellent preservation of the mucosal villi were seen in most specimens (Fig. 5). These are long, wavy, fingerlike, slender projections lined by very regular columanr epithelium containing elongated nuclei situated towards the base of the cells. The rest of the cells are filled with a homogeneous material staining pink in the hematoxylin-eosin preparations. Mitosis is not seen in the nuclei of the villous epithelium. A well defined

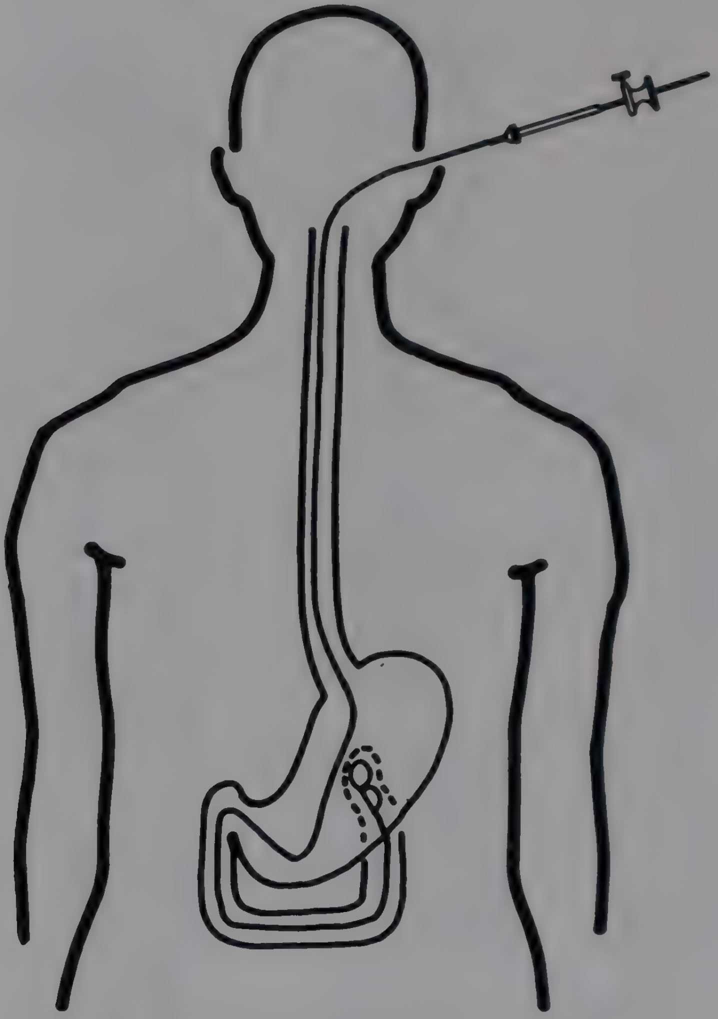


FIG. 4: Tube in proximal part of jejunum.

basement membrane lines their undersurface and a brush border can be seen clearly at their free surface. Goblet cells are scattered among the covering epithelium. In the glandular layer of the mucosa (Fig. 6) the villous epithelium forms the crypts and glands of Lieberkuhn. These are composed of columnar cells, somewhat shorter than those of the villi and containing ovoid nuclei. Mitosis is conspicuous within the nuclei of the glandular epithelium. The appearances of active mitosis of the cells of glands and crypts of Lieberkuhn and their absence in the villous epithelium lend support to the observations made by Vitale et al, Grampa and Dustin, and Le Blond and Stevens, that the former cells are precursors of the latter (villous) cells (1–3). Goblet cells are more numerous in the glands of Lieberkuhn, and Paneth and argentaffin cells can be clearly seen within the glands in hematoxylin-eosin preparations. The interstitial connective tissue contains plasma cells, lymphocytes, histiocytes, eosinophils and occasional mast cells and neutrophil polymorphs. The more detailed histology of the small intestinal mucosa and variations from the normal have been described by Doniach and Shiner (4).

HISTOPATHOLOGIC FINDINGS IN THE MALABSORPTION SYNDROME

The controversy over histologic changes in the small intestines in sprue has been raging for more than half a century. The difficulties were accentuated by

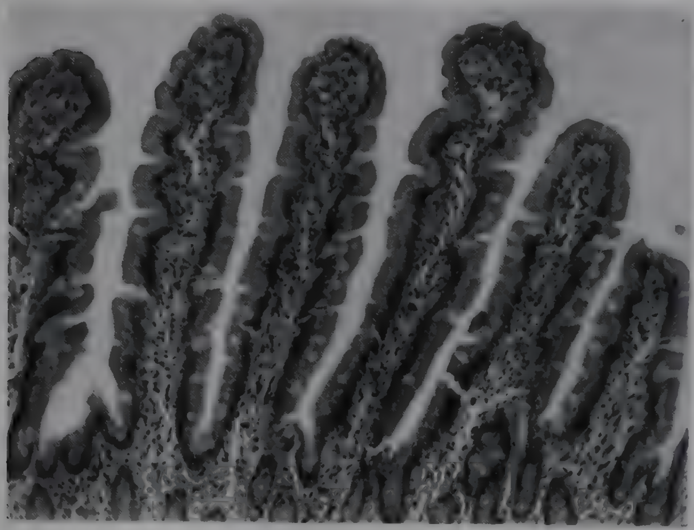


FIG. 5: Normal jejunal villi. H. & E. ×175.

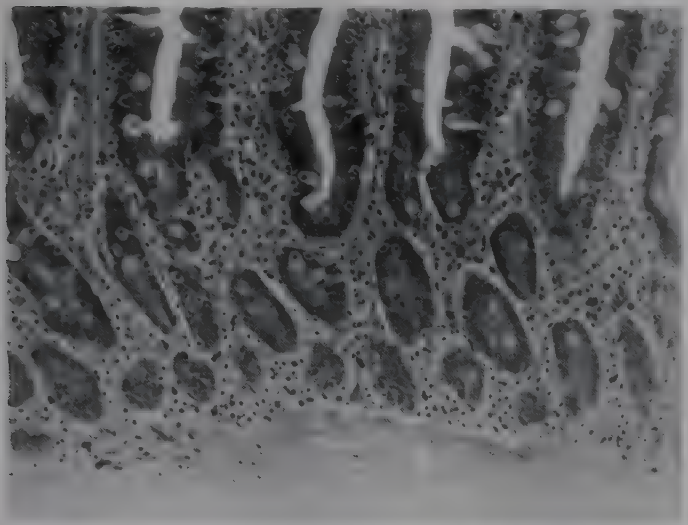


FIG. 6: Glandular layer of jejunal mucosa, showing normal glands of Lieberkuhn. H. & E. ×235.

the fact that as so few cases came to laparotomy, the evidence for pathological changes in the gut had to be obtained from the post-mortem room and, due to the rapid setting in of autolysis, the small intestine is notoriously difficult to study after death. Thus Wethered, who found atrophy of the small intestine in sprue, expressed considerable doubt as to the validity of his post-mortem findings (5). On the other hand, Thaysen, in 1931 and 1934, could find no evidence of any histologic changes attributable to sprue and his views have become accepted up to this present day (6). Various workers, notably Manson-Bahr, found ulceration in the small intestine (7). Others, like Mackie and Fairley, considered that there were degenerative, non-inflammatory changes in the villi leading eventually to shrunken and acellular villi and degeneration of the glands of Lieberkuhn with thinning of the wall of the small intestine (8). Mucosal and submucosal round cell infiltration of the small intestine were found in other cases (9). Schein in 1947 described a post-mortem case of idiopathic, non-tropical sprue in which he found clubbing and mushrooming of the small intestinal villi in the tip of which hyaline material was deposited (10).

Adlersberg and Schein in their study of six autopsied cases of idiopathic sprue observed that several anatomic findings, while not necessarily characteristic or pathogenetically significant, were encountered at autopsy in cases of sprue (11).

Atrophy of the small intestinal mucosa and villous deformities consisting of flattening and blunting of the villi (clubbing) as well as increased cellularity of the lamina propria were noted. They described instances of hemofuscinosis of the muscularis of the gastrointestinal tract, chronic mesenteric lymphadenitis with replacement of lymphatic tissue by hyaline and fibrous bands, centrolobular fibrosis of the liver and various degrees of pancreatic fibrosis (in the absence of biliary disease). Although it is apparent that these changes in the bowel and mesenteric lymph nodes are such as to impair absorption the more fundamental pathogenetic implications were not clear.

In 1949, Paulley obtained biopsy specimens by laparotomy of 3 cases of idiopathic, non-tropical sprue and came to the conclusion that the absorptive defect was due to flattening of the villi and infiltration of the mucosa and submucosa with chronic inflammatory cells. He described a picture of non-specific jejunitis (12).

Many theories have been put forward as to the reason for the possible defect in absorption in the sprue syndrome, none of them satisfactory. Thus bacterial invasion, edema, circulatory changes and allergy have all been suggested. With the method of obtaining small intestinal biopsies by the oral route, it is hoped that many doubts as to the underlying histopathologic defect in sprue will be cleared up. From the study of the histology of the mucosa of the upper small intestine in 17 cases of sprue which, with the exception of one case, was obtained by the biopsy tube method, a few findings are summarized:

1. Histologic changes in the small intestine in sprue occur in some cases but not in all.
2. These changes are non-specific and consist of mucosal, chiefly villous atrophy. With the exception of one case of pernicious anemia, which has not been further investigated, mucosal atrophy has so far been observed only in sprue and not in 12 small intestinal biopsies obtained from patients with small and large intestinal tract disease and 15 control cases. The former group consisted of four patients with ulcerative colitis, two with regional ileitis, five with non-specific diarrhea and one with post-gastrectomy [dumping] syndrome. The latter group consisted of four patients with x-ray negative dyspepsia, six with gastric ulcer, two with cirrhosis of the liver, one with congenital hemorrhagic telangiectasis, one with paroxysmal nocturnal hemoglobinuria and one with "posthepatitis syndrome".
3. Histologic changes in the small intestine were seen mainly in idiopathic non-tropical sprue, tropical sprue and a possible case of celiac disease.
4. A repeat biopsy on one case of idiopathic, non-tropical sprue showing abnormal mucosa was carried out and revealed identical mucosal changes. This suggests that the disease process must affect a considerable portion of the upper small intestinal mucosa and that, although the patient was in clinical remission and under treatment with folic acid at the time the second biopsy was taken, the histopathologic pattern remained unchanged.
5. Another case of idiopathic, non-tropical sprue who came to laparotomy shortly after small intestinal biopsy by the oral route was performed had

TABLE I

Varieties of steatorrhoea and degree of involvement of small intestinal mucosa

Idiopathic Non-Tropical	Histology	Tropical	Histology	Pancreatic	Histology	Post-Gastrectomy	Histology	Miscellaneous	Histology
Case 1	Severe atrophy	Case 10	Severe atrophy	Case 17	Normal	Case 14	Normal	Case 11—post-gastrect., but probably idiopathic	Severe atrophy
2	Partial atrophy					15 16	Normal Normal	Case 12—secondary to tuberculosis? idiopathic?	Partial atrophy
3	Partial atrophy							Case 13—secondary to chylous obstruction	Partial atrophy
4	Severe atrophy								
5	Severe atrophy								
6	Severe atrophy								
7	Severe atrophy								
8	Severe atrophy								
9	Severe atrophy								

TABLE II

Clinical data of 17 patients with steatorrhea and the degree of involvement of small intestinal mucosa

Case	Sex	Age	Duration of symptom in years	Etiology	Diarrhea	Wt. Loss	Hb. %	FF	PP	GTT	Small Bowel Study	Bone Marrow	Histology
1. A. C.	F	61	½	Idiopathic	Gross	28 lbs.	76%	14	—	Normal	Clumping	Megaloblastic	Severe atrophy
2. J. M.	M	62	2	Idiopathic	None	Slight	43%	47.6	—	—	Normal	Megaloblastic	Partial atrophy
3. E. B.	F	64	3	Idiopathic	None	Moderate	72%	34	—	Flat	Normal	Normal	Partial atrophy
4. L. B.	M	25	20	Idiopathic	Moderate	50 lbs.	90%	Slight increase	5.6	Flat	Clumping	—	Severe atrophy
5. N. F.*	M	46	14	Idiopathic	Gross	Gross	36%	Gross increase	—	Flat	Clumping	—	Severe atrophy
6. P. S.*	M	58	25	Idiopathic	Gross	40 lbs.	80%	62.4	7.0	Flat	Clumping	—	Severe atrophy
7. S. H.*	F	72	21	Idiopathic	Gross	39 lbs.	32%	56.5	3.6	Flat	Clumping	Normal	Severe atrophy
8. C. N.*	F	46	45	Idiopathic	Gross	38 lbs.	86%	Gross increase	5.6	Flat	Clumping	—	Severe atrophy
9. L. W.	F	15	2	Idiopathic	Mild	33 lbs.	22%	8.6	4.3	Flat	Clumping	Megaloblastic	Severe atrophy

10. R. W.	F	54	¾	Tropical sprue	Gross	10 lbs.	68%	16.2	5.4g	Flat	Clumping	Megaloblastic	Severe atrophy
11. J. J.	M	65	1	Idiopathic ? Post-gastrectomy	Gross	27 lbs.	68%	46.8	4.7	—	Clumping	Megaloblastic	Severe atrophy
12. H. W.	M	55	½	? Secondary ? Idiopathic	Gross	30 lbs.	70%	27	—	—	Clumping, distension	Macronormoblastic	Partial atrophy
13. G. E.	M	42	10	Secondary, chylous obstruction	Moderate	None	60%	7.7	6.0	Normal	Normal	Normal	Normal
14. R. P.	M	50	8	Post-gastrectomy	Moderate	Moderate	92%	10.7	—	—	Rapid emptying	—	Normal
15. S. F.	M	51	1	? Post-gastrectomy ? Idiopathic	Gross	42 lbs.	95%	30	4.0	—	Clumping	—	? Normal
16. G. A.	M	56	⅓	Post-gastrectomy	None	?	33%	47.6	—	—	Normal	Megaloblastic, iron def.	Normal
17. M. V.	F	63	7/12	Pancreatic steatorrhea	Moderate	39 lbs.	76%	Sudan III positive	5.6	Diabetic	Normal	Iron def.	Normal

FF = Fecal fat expressed as percentage of dry fecal weight.
PP = plasma proteins in gm./100 ml. of serum.
GTT = glucose tolerance test curve.

* Therapy resistant; prolonged steroid therapy resulted in subsidence of diarrhea, improvement of steatorrhea and considerable weight gain.

two biopsies taken from the terminal ileum. These showed changes of mucosal atrophy similar to those seen in the upper small intestine.

6. Four cases studied at The Mount Sinai Hospital in New York were controlled on steroid therapy, prior to being subjected to biopsy by the oral route. These four patients showed the severest pathologic changes of the mucosa, indicating that, despite marked clinical improvement after administration of steroids, improvement from the histopathologic point of view is not seen.

Table I shows the various types of malabsorption syndrome into which the 17 patients so far studied fell and the degree of mucosal changes. It will be seen that gross mucosal changes, with the possible exception of one case, were seen only in the idiopathic, non-tropical sprue and in tropical sprue. These cases comprised a total of 10 patients. In the post-gastrectomy (3 patients) and pancreatic (1 patient) types of steatorrhea the small intestinal mucosa was found normal. One case of steatorrhea secondary to chylous obstruction likewise showed no abnormal mucosal changes. But two other patients (of whom one may be considered a case of steatorrhea secondary to tuberculous enteritis, and the other a possible case of post-gastrectomy steatorrhea, although there was

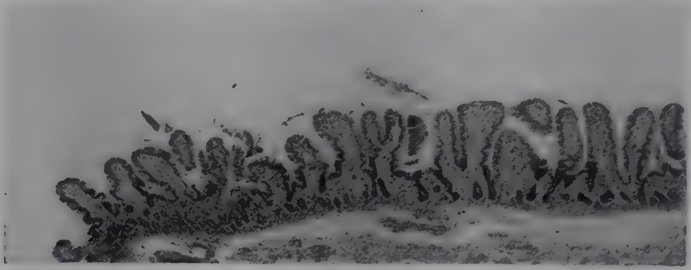


Fig. 7: The jejunal villi in non-tropical sprue, showing clubbing and mushrooming. H. & E. ×55.

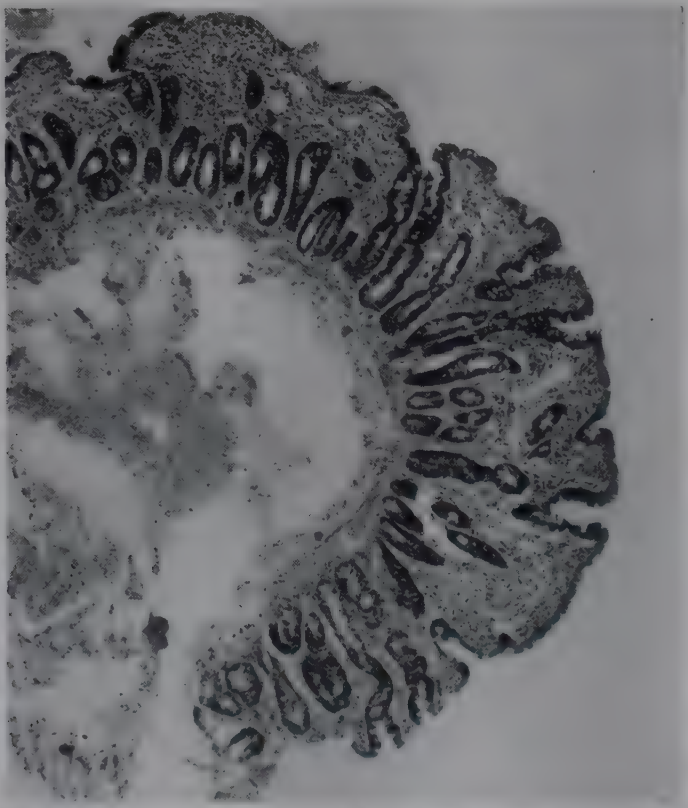


Fig. 8: The jejunal villi in non-tropical sprue showing almost total flattening. H. & E. ×55.

evidence that steatorrhea might have been present before gastrectomy) showed mucosal atrophy, which was more severe in the second.

Mucosal changes varied from partial atrophy, in which the main abnormalities observed consisted of blunting and reduction in the size of the villi and therefore a total reduction of villous surface area, to gross and severe atrophy in which the villi were almost totally flattened and the cells of the surface epithelium and crypts and glands of Leiberkuhn showed atrophic changes.

Villi. Changes from clubbing and mushrooming (Fig. 7) to almost total flattening (Fig. 8) were observed. There was considerable variation in size and shape of villi within the same biopsy in the milder cases, but in the severe cases a uniform flattening and almost total obliteration of villi was seen. The surface epithelium covering the villi showed striking changes which were mainly confined to the severely atrophic mucosa. Instead of the regular, tall, columnar type of cells with elongated, dark staining muclei situated more basally and a pink staining homogeneous cytoplasm, the cells were reduced in size to low columnar cells with small irregular nuclei and vacuolated cytoplasm. The basement membrane appeared interrupted or totally absent, but the brush border seemed always intact (Fig. 9). Goblet cells were more numerous in the villi in some biopsies but this was not a universal picture. The villous stroma showed no striking abnormalities apart from edema and congestion in some biopsies and moderate increase in cellular infiltration, consisting mainly of lymphocytes, plasma cells, eosinophils and occasionally polymorph neutrophils, in others. The flattening of villi, accentuated by the edema observed in some biopsies, imparted an impression of increase in thickness of the lamina propria of the glandular layer of the mucosa.

Crypts and glands of Lieberkuhn. Gaping crypts and distended glands were seen in many specimens though not in all (Fig. 10). In these the epithelium was flattened and the nuclei were irregular in size. In some cases mitosis was reduced. Goblet cells were numerous in some specimens where they contained deep blue-staining material in hematoxylin-eosin preparations. It must be pointed out that normal variation of the glandular epithelium is so common that, although it was more frequently seen in atrophic mucosa, it was difficult to correlate glandular abnormalities with overlying cellular atrophy in the villi. Cellular infiltration of

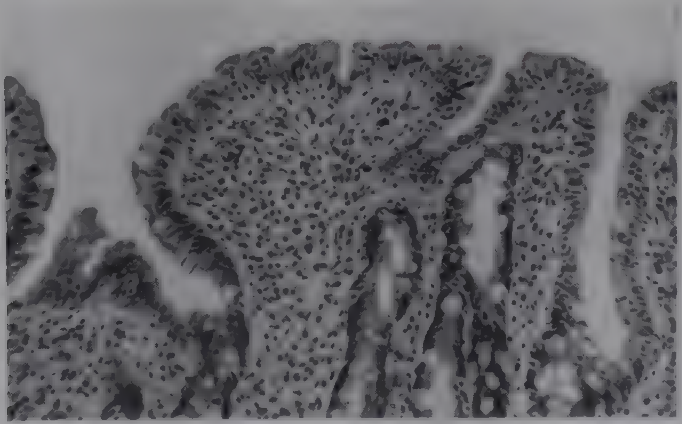


FIG. 9: High power view of clubbed villi showing irregular nuclei and vacuolated cytoplasm of surface epithelium. The basement membrane seems interrupted in places but the brush border is well preserved. H. & E. ×300.

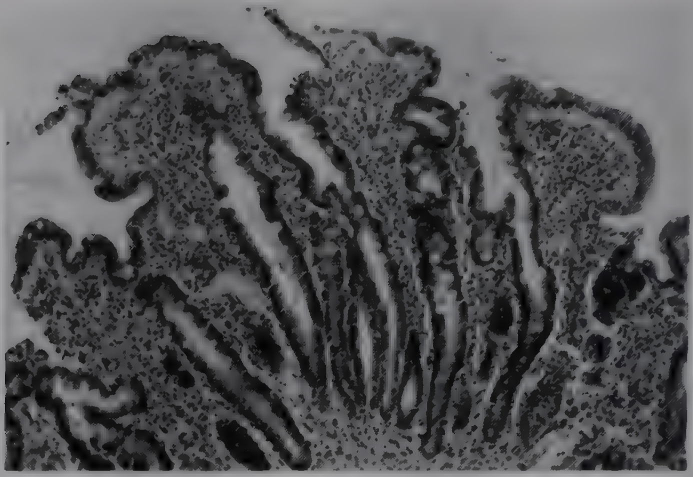


FIG. 10: Jejunal mucosa in tropical sprue showing gaping and distended glands of Lieberkuhn with flattened epithelium and irregular nuclei, also some increase in goblet cells. H. & E. ×300.

the glandular layer was increased in some specimens and was of the same variety as in the villi.

DISCUSSION

Evidence has been presented that mucosal, though mainly villous, atrophy of the small intestine is a feature of idiopathic sprue and has been found in all cases of idiopathic non-tropical sprue, in one case of tropical sprue and in a possible case of celiac disease. As yet the number of cases with secondary varieties of sprue which were biopsied is too small to allow us to state that no abnormal mucosal changes are seen here. It is at times extremely difficult if not impossible to differentiate between a secondary type of sprue and a latent primary sprue reactivated by intestinal disease or alteration in the intestinal mechanics. It is conceivable that mucosal atrophy is not a uniform process along the whole of the small intestine or that it varies in degree from site to site. This was emphasized by Paulley who found patchy atrophy of the small intestinal mucosa postmortem in a case of seemingly idiopathic, non-tropical sprue who had also had a partial gastrectomy with exacerbation of his steatorrhea (13). Jejunal biopsy carried out one year after partial gastrectomy showed normal mucosa.

The etiology of idiopathic sprue still remains obscure. Most observers class celiac disease, idiopathic non-tropical sprue and tropical sprue as one and the same disease occurring at different phases of life and requiring certain trigger mechanisms for its activation (14). The absorptive defect is considered due to congenital and hereditary abnormalities. This theory seems to be widely accepted on the grounds that celiac disease occurs in families and that many celiac children, after variable periods of remission, develop the adult type of sprue (15). Case 9 is the youngest case of "idiopathic sprue" in this series, and Cases 4 and 8 gave a clear history of celiac disease in childhood. Yet the histopathologic changes in these patients differed in no way from those found in patients with idiopathic, non-tropical sprue in whom no history of celiac disease was obtainable. Accepting the common histologic bond between celiac disease, adult idiopathic non-tropical sprue and tropical sprue, one might postulate that the congenital and hereditary defect consists perhaps in primary atrophy of the small intestinal mucosa or some underlying mucosal defect which eventually leads to secondary atrophy. Final proof might be obtained when small intestinal biopsies are taken in children with celiac disease. An interesting finding is the discrepancy between villous and glandular atrophy in the biopsies of patients on steroids as compared with the uniform atrophy affecting both villi and glands in those cases not receiving steroids. It is possible that hormone therapy influences cellular regeneration in some way thereby improving absorption at least to some extent.

SUMMARY

A method of taking small intestinal biopsies has been described and the histopathologic changes affecting the small intestinal mucosa in 12 patients with the malabsorption syndrome have been demonstrated.

ACKNOWLEDGMENTS

My grateful thanks are due to Dr. F. Avery Jones, London, and Dr. D. Adlersberg, New York City, for permission to biopsy and study their cases; to Dr. I. Doniach for his advice in the preparation of this paper; also to Miss Y. Vincent for the photomicrographs and to Mr. J. E. Mayhew for histological preparations.

This work has been supported by a grant from the Medical Research Council (England).

REFERENCES

1. Vitale, J. J., Zamcheck, N., DiGiorgio, A. B. and Hegsted, D. M.: Effects of Aminopterin Administration on the Respiration and Morphology of the Gastrointestinal Mucosa of Rats. J. Lab. & Clin. Med., 43: 4, 1954.
2. Grampa, G., and Dustin, P. Jr.: Analyse par la Colchine, des Effets Radiomemetique de l'Acide 4-Amino-Pteroyl Glutamique. Rev. Belge Path. et Med. Exper., 22: 113, 1952.
3. Le Blond, C. P., and Stevens, L. E.: The constant renewal of the intestinal epithelium in the albino rat. Anat. Rec., 100: 357, 1948.
4. Doniach, I., and Shiner, M.: Histology of Duodenal and Jejunal Biopsies. Gastroenterology. In press.
5. Wethered, B.: Psilosis or Sprue. Trans. Path. Soc. London, 62: 116, 1890.
6. Thaysen, T. E. H.: Pathological Anatomy of the Intestinal Tract in Tropical Sprue. Trans. Roy. Soc. Trop. Med. and Hyg., 24: 539, 1931.
   Thaysen, T. E. H.: La Steatorrhee Idiopathique, la Sprue Tropical et Non Tropical et l'Infantilisme Intestinal. Arch. de Mal. de L'app. Digestif, 24: 123, 1934.
7. Manson-Bahr, P.: The Morbid Anatomy and Pathology of Sprue. Lancet, 1: 1148, 1924.
8. Mackie, F. P., and Fairley, N.: Morbid Anatomy of Sprue. Indian Journal Med. Res., 16: 799, 1929.
9. Bahr, P. H.: Sprue. Brit. Med. J., 2: 17, 1914.
10. Schein, J.: Syndrome of Non Tropical Sprue with hitherto Undescribed Lesions of the Intestine. Gastroenterology, 8: 4, 438, 1947.
11. Adlersberg, D., and Schein, J.: Clinical and Pathological Studies in Sprue. J.A.M.A., 134: 1459, 1947.
12. Cullinan, E. R., Gill, A. M., and Paulley, J. W., Discussion on Chronic Diarrhoea, excluding Tropical Causes. Proc. R. Soc. Med., 42: 235, 1949.
13. Paulley, J. W.: Observations on Postgastrectomy Steatorrhea and a Case of Patchy Jejunal Atrophy. Lancet. In press.
14. Thaysen, T. E. H.: Non Tropical Sprue. Oxford University Press, 1932.
    Di Sant'Agnese, P. A.: Malabsorption Syndrome. Am. J. Med., 15: 790, 1953.
15. Andersen, D. H., and Di Sant'Agnese, P. A.: The Celiac Syndrome. In Brenneman "Practice of Pediatrics", Vol. 1., Chap. 29., 1957.

CLINICAL ASPECTS OF THE MALABSORPTION SYNDROME (IDIOPATHIC SPRUE)

Observations in 94 Patients

ELAINE T. BOSSAK, M.D.
CHUN I. WANG, M.D.
AND
DAVID ADLERSBERG, M.D.
New York, N. Y.

In the broader concept of today, the malabsorption syndrome (idiopathic sprue) is a genetically transmitted complex metabolic disorder (1). The defect of absorption represents the main clinical abnormality; however, sprue is more than defective intestinal absorption. It may start early in life or remain latent for many years and become manifest during adult life. It appears now that celiac disease in children, as well as tropical and non-tropical sprue and idiopathic steatorrhea in adults, are clinical manifestations of the same basic metabolic disturbance, chiefly characterized by impaired intestinal absorption (2–5). Many environmental factors such as the stress of tropical climates, tropical and non-tropical infections, malnutrition, underweight, certain medicaments (antibiotics) and perhaps psychological disturbances are precipitating or "triggering" mechanisms converting a predisposed person with "latent sprue" into a patient with symptoms and signs of "manifest sprue" (6).

In idiopathic (primary) sprue there are no specific gross changes in the gastrointestinal tract although some abnormalities have been observed in advanced instances of this disorder in post-mortem studies and in biopsies. In contrast, secondary sprue, which may simulate the idiopathic form in its clinical manifestations, is caused by severe gross disease of the small bowel such as lymphosarcoma, amyloidosis, intestinal lipodystrophy (Whipple's disease) and certain forms of jejuno-ileitis. Malabsorption syndromes resulting from extensive resection of the small bowel, a gastro-jejuno-colic fistula, or inadvertent gastroileostomy following subtotal gastrectomy, as well as steatorrhea due to pancreatic disease or resection, must be also differentiated from idiopathic sprue (7, 8).

The present study is a review of 94 patients with idiopathic sprue observed at The Mount Sinai Hospital from 1931 to 1956. The patients all had primary sprue established by clinical and laboratory evidence. They revealed at some time all or most of the typical features of this syndrome as described later. They had no roentgenologic or other evidence of *gross* organic disease in the gastrointestinal tract. They have been selected for this study from a larger group of patients because of prolonged observation (average follow-up period over five years).

From The Department of Medicine, The Mount Sinai Hospital, New York, N. Y.

GENERAL CONSIDERATIONS

The group included 32 men and 62 women. The predominance of women in the present series was also observed in the earlier report from this hospital (7). This has not been noted in most other reviews where the sex incidence was approximately equal (4, 9, 10). Manson-Bahr (11) noted a slightly larger number of women with tropical sprue.

The age at time of first observation ranged from 16 to 73 years with a mean of 45 years. The average age of the patients was the same in men and women (Table I). This is in agreement with observations published from England concerning idiopathic steatorrhea (4). Sprue has been observed at all ages with the usual median at about age 40 years (4, 5, 7, 12). Eight men and 15 women were Puerto Ricans who had lived for varying periods of time in New York.

The duration of symptoms when first seen ranged from one month to 52 years with a mean duration of 7.2 years. The long duration of symptoms prior to hospitalization has been noted by previous reviewers (13–15). The insidious onset of the disorder, the vagueness of symptoms and the tendency to spontaneous remissions led to delay in seeking medical aid and postponement of proper diagnosis. The duration of subsequent observation ranged from a single hospitalization (12 patients) to 22 years, with a mean follow-up period on 82 patients of 5.2 years.

Nineteen patients died, five men and 14 women, with an over-all mortality of 20.2 per cent (15.6 per cent in men, 22.6 per cent in women). Six patients died of progressive cachexia, in one instance terminating in thromboses of the dural sinuses and cerebral veins after an episode of severe tetany. In three patient respiratory infections were the immediate cause of death; acute necrotizing laryngotracheitis led to death in one and bronchopneumonia in two. In two patients severe bleeding was the immediate cause of death, associated with acute yellow atrophy of the liver in one. In two patients acute intestinal obstruction due to volvulus of the sigmoid was observed. This was the cause of death in one patient, while the other succumbed to acute pyelonephritis following resection of the sigmoid. Two patients with long-standing sprue succumbed to gastric carcinoma. One patient died of superimposed hepatic insufficiency. One patient died after an appendectomy for acute appendicitis. One patient at death had extensive ulceration of the small intestine. One patient (sprue in remission) died in an old age home of heart failure. Post-mortem examinations were performed in 14 patients. Eleven of these will be presented in detail elsewhere in this symposium (16).

TABLE I

Age of patients when first seen

Age (Yrs.)	0–20	21–30	31–40	41–50	51–60	61–70	>70
Males..........	1	6	6	7	5	5	2
Females........	0	13	9	15	17	8	0
Total........	1	19	15	22	22	13	2

SYMPTOMATOLOGY

The symptoms presented below are given in their order of frequency (Fig. 1). The most frequent complaints were the triad of diarrhea (94.6 per cent), weakness (88.3 per cent) and weight loss (84.1 per cent). Over one-third of the patients with diarrhea (36.3 per cent) had more than six bowel movements a day. Diarrhea was intermittent with a greater incidence of watery stools (43.8 per cent) during the period of acute symptoms than of the classical, pale, bulky stools (30.3 per cent). The character of the diarrhea was not adequately described in 20.5 per cent. Normal appearing bowel movements were present at all times in 4.2 per cent of patients while 1.2 per cent were constipated. These patients may fall in the group termed latent or occult steatorrhea (17, 18) or incomplete sprue (11).

Loss of weight ranged from seven to 60 pounds with a mean weight loss of 25.3 pounds. This degree of weight loss was comparable to those given by others (2, 4, 5, 7, 11). The majority of the patients (70.1 per cent) lost more than 15 pounds at some time in the course of their illness. Weight loss of as much as 50 per cent of the normal body weight has been observed by us and by others (5, 7, 13, 14).

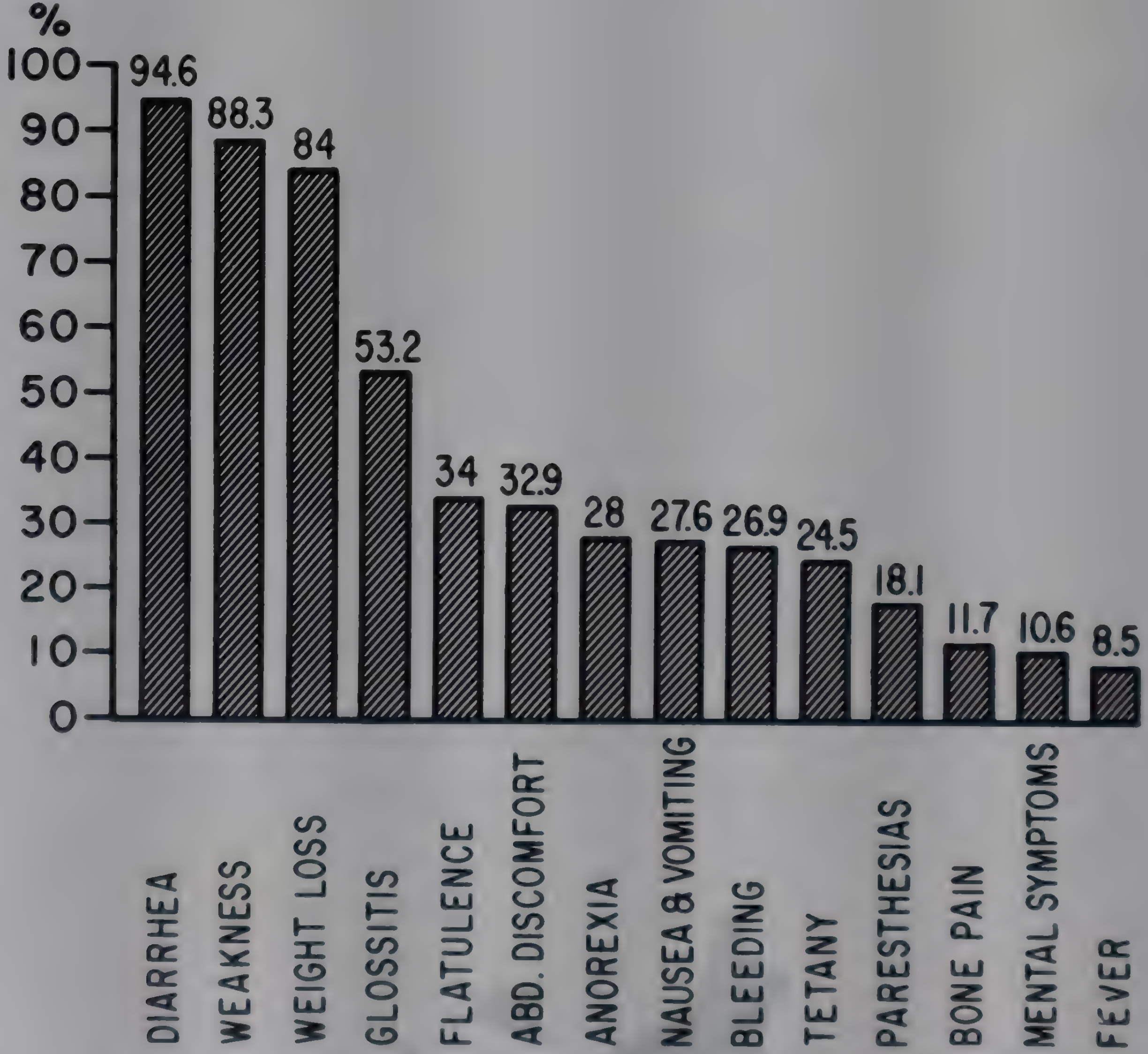


FIG. 1. Major symptoms observed in 94 patients with idiopathic sprue.

Glossitis and stomatitis of some degree was noted in 53.2 per cent of patients. The incidence was lower than that reported in previous reviews (7, 9, 11). The explanation may lie in the generally improved diet in more recent years resulting in lower occurrence of vitamin deficiencies. Recent reports from Havana and Puerto Rico have indicated a lower incidence of tropical sprue in these countries in recent years. This change has also been attributed to the improved nutrition of the population (19). That glossitis in sprue is not exclusively a result of avitaminosis B has been noted by others (15), so this may not be the sole explanation for the reduced incidence of this symptom.

Vague abdominal discomfort (pain, burning, cramps), flatulence, nausea and vomiting were noted by almost all of the patients. Severe abdominal pain, however, was uncommon and when present usually indicated major complications such as intestinal obstruction (volvulus), bleeding or an intercurrent disease, i.e., cholecystitis, appendicitis. Anorexia was found in about 25 per cent of patients. Voracious appetite, noted by Thaysen (2, 20) and Cooke (4) in their series, was not a prominent feature and was noted only in milder cases or after the patients showed clinical improvement.

Hemorrhagic manifestations were noted in 26.6 per cent of patients, a higher incidence than previously noted. They varied in severity from skin petechiae to fulminating gastrointestinal hemorrhage. These cases are reported in greater detail elsewhere in this symposium (21).

Tetany was observed in 24.5 per cent of patients; this incidence compares well with the occurrence reported by other observers (5, 7). Bone pain was complained of by 11.7 per cent. Tetany occurred usually in patients who were suffering a severe exacerbation. The comparatively low incidence of clinical tetany, as compared to the presence of low serum calcium levels, may be related to the associated hypoproteinemia which results in relatively higher levels of ionized calcium in the serum. Paresthesias were present in 18.1 per cent.

Severe mental changes occurred in 11 patients. In five instances there was frank psychosis (one patient was on steroid therapy (22)), and the remaining six patients exhibited varying degrees of depression, anxiety or character disorders.

Subnormal body temperature was more common than low grade fever; definite fever was usually associated with intercurrent infections. Patients with sprue have a diminished resistance to infection even during remission. It has also been observed that infections, seemingly innocuous, often precipitate a relapse of the disease (7). There were some instances of unexplained temperature elevations.

SIGNS

The observed signs are summarized in order of frequency in Figure 2. Emaciation was the most common sign (64.9 per cent). The initial body weight ranged from 67 to 167 pounds; the mean weight was 104 pounds (males 116 pounds, females 98 pounds). A large number of patients showed abdominal distention (37.2 per cent) and dependent edema (36.2 per cent). The former was due mostly to distended loops of small bowel which not infrequently were visible on the abdominal wall. Distention due to ballooning of the colon was also observed frequently. Ascites, as part of anasarca, was rare (two patients).

Hepatomegaly occurred in 30.8 per cent of the group. The enlargement of the liver was usually not more than one to two finger's breadth below the costal margin. Splenomegaly of mild degree was present in 6.3 per cent. The higher incidence of hepato-splenomegaly, as compared with the observations of others (12), was probably caused by the large number of Puerto Rican patients in whom parasitic infestation was common.

The mean systolic blood pressure (64 patients) was 105 millimeters of mercury. In 28.9 per cent of this group the systolic blood pressure was below 100 millimeters of mercury. Hypotension was a feature which persisted during remission as has been seen by others (2, 20). Clubbing of fingers and/or toes was found in 22.3 per cent, a figure unchanged from the previous study.

Less common manifestations were pigmentation (11.7 per cent) and dryness (9.6 per cent) of the skin. In some instances the pigmentation was extensive and included the lips and buccal mucosa. Dry skin was often a manifestation of vitamin A deficiency. No instances of pellagra were encountered. The decreased

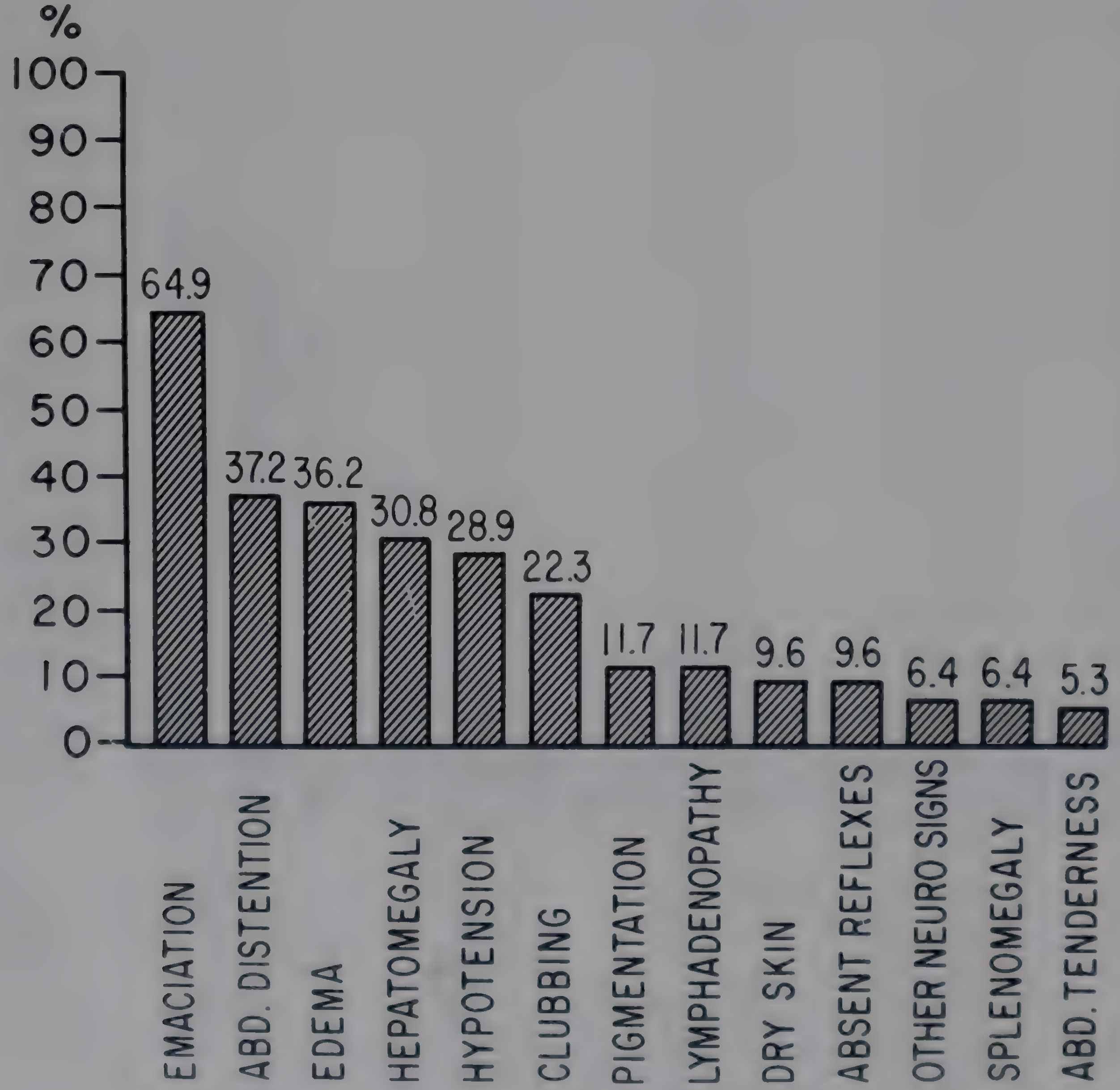


Fig. 2. Major signs observed in 94 patients with idiopathic sprue.

incidence of these signs compared with the earlier study may be related again to the improved nutritional state of the population.

Abnormal neurologic signs were present in 16.0 per cent of patients. Absent deep tendon reflexes was the commonest finding. Lesions of the central nervous system with severe disability were also encountered and were similar to those described by other observers (5, 9, 11, 12). Three patients presented varying manifestations of posterior and lateral column involvement. In none was there histamine-achlorhydria. One patient (with a history of lues) had a clinical picture of cervical tabes. One patient had a transient Brown-Séquard syndrome. These neurologic findings are presented in detail elsewhere in this symposium (23).

Moderate lymphadenopathy was noted in 11.7 per cent of patients. Abdominal tenderness occurred only in 5.3 per cent and was thus rare in uncomplicated sprue.

HEMATOLOGIC PICTURE

The hematologic findings in these patients are presented in Table II and III. The peripheral blood picture of sprue is characterized by anemia which is often macrocytic and associated with a megaloblastic bone marrow. In many instances, however, iron deficiency anemia may be a prominent feature with an erythroid marrow (24). Impairment of iron absorption has been demonstrated in studies

TABLE II

Laboratory data in sprue patients

Determination	No. of Patients	Mean	Range
Hemoglobin (gm.%)	81	9.3	2–14.9
Red blood count (M/cu.mm.)	73	3.1	0.66–4.8
White blood count (/cu.mm.)	75	5,918	1700–12,800
ESR (mm./hr.)	25	29.3	3–104
Gastric acidity (units)	45	42.3	0– >100
Total protein (gm.%)	62	5.7	3.4–7.7
Albumin (gm.%)	55	3.3	1.7–4.7
Sodium (mEq./l.)	18	138.4	128–145
Potassium (mEq./l.)	18	4.2	1.8–5.5
Calcium (mg.%)	69	8.1	4.4–11.4
Phosphorus (mg.%)	57	3.0	1.2–4.6
Alkaline phosphatase (K-A units)	38	16.5	5.4–44.0
Fasting blood sugar (mg.%)	65	79.3	45–115
Total cholesterol (mg.%)	76	162	80–340
Esterified cholesterol (mg.%)	31	112	61–173
Phospholipids (mg.%)	42	203	93–315
Total lipid (mg.%)	42	584	175–1110
Vitamin A (µg.%)	55	31.3	0–124
Carotene (µg.%)	55	56.3	0–420
Vitamin B_{12} excretion (%)	23	2.9	—
Fecal fat, total (%)	54	38.0	11.2–71.6
Fecal fatty acid (%)	26	25.4	8.2–44.3

TABLE III

Incidence of abnormal laboratory data in sprue patients

Anemia (Hb. < 5 gm.%)	14.1%
(Hb. < 10 gm.%)	51.5%
(RBC < 3.5 million/cu.mm.)	55.4%
Megaloblastic bone marrow	33.3%
Erythroid bone marrow	20.0%
Leukopenia (WBC < 5,000/cu.mm.)	37.3%
Anisocytosis	37.3%
Hypoprothrombinemia	70.2%
Elevated sedimentation rate (>30 mm./hr.)	28.1%
Thrombocytopenia (<100,000/cu.mm.)	13.2%
Achlorhydria	13.1%
Hypoproteinemia (<5 gm.%)	19.4%
Hypoalbuminemia (<3.5 gm.%)	51.7%
Hypoglycemia (<70 mg.%)	12.2%
Hypocalcemia (<9.0 mg.%)	66.2%
Hypokalemia (<3.5 mEq./l.)	16.7%
Hypophosphatemia (<2.5 mg.%)	28.3%
Increased alk. p'tase (>10 K-A units)	61.5%
Hypocholesteremia (<150 mg.%)	50.0%
Hypophospholipidemia (<200 mg.%)	59.5%
Hypolipemia (total lipids < 500 mg.%)	40.5%
Abnormal liver chemistries	21.4%
Flat glucose tolerance test	92.0%
Flat vitamin A tolerance test	81.1%
Diminished vitamin B_{12} absorption	87.0%
Steatorrhea (>15%)	93.1%
(>25%)	75.9%
Abnormal pancreatic function	14.3%
Small bowel "sprue pattern"	87.3%
Osteoporosis (osteomalacia)	59.5%

with radioactive isotopes (25). In 51.1 per cent of patients the hemoglobin level was less than 10 gm. per cent and in 14.1 per cent was below 5. The mean level was lower than those noted in other series (4, 7). In the majority of patients (63.0 per cent) the red blood count was below 3.5 million per cu. mm. Macrocytes were present in 37.3 per cent of 67 patients. Leukopenia (white blood count below 5,000 per cu. mm.) was noted in 37.3 per cent. Thrombocytopenia (platelets below 100,000 per cu. mm.) was noted in 13.2 per cent (53 determinations). The high incidence of leukopenia and thrombocytopenia may reflect the interaction of multiple deficiencies such as vitamin B_{12} folic acid and iron. No instances of aplastic anemia were encountered as has been observed in tropical sprue (26).

The bone marrow was studied in 30 patients and was normal in 36.7 per cent, megaloblastic in 33.3 per cent, erythroid in 20.0 per cent and showed other non-diagnostic alterations in 10.0 per cent. In the 10 patients with megaloblastic bone marrow, only one had associated achlorhydria. Because of the limited number of bone marrow aspirations these figures cannot be assumed to be generally representative of the bone marrow in sprue.

The prothrombin time was determined in 37 patients and was prolonged more than three seconds over the control sample in 70.2 per cent. This high incidence of hypoprothrombinemia may be correlated with the large number of hemorrhagic phenomena observed in the present group of patients. Again, this determination was done most often in cases where a history of bleeding was obtained so that a true incidence of hypoprothrombinemia in sprue was not obtained.

Gastric analysis yielded a 13.1 per cent incidence of histamine-achlorhydria. The mean free acid concentration was 42.3 units. These figures come close to those noted in the earlier survey from this hospital (7). This figure coincides with the incidence of achlorhydria in a normal population of comparable age (14) and suggests that achlorhydria is not an essential feature of the sprue syndrome, in contrast to pernicious anemia.

BLOOD CHEMICAL STUDIES

The chemical blood analyses reflected the malnourished state of the patients. Hypoproteinemia, hypoalbuminemia, hypoglycemia and hypolipidemia occurred in a large number. The levels observed coincided with figures given in the previous review and by others (5, 7, 11, 20, 27).

Serum total proteins were low (Table II and III) and in 57.7 per cent the serum albumin was below 3.5 gm. per 100 ml., a considerably higher proportion of hypoalbuminemia than was seen in England (4). This may be a reflection of a more severe disorder observed in the present group of sprue patients.

There was a high incidence of hypocalcemia (66.2 per cent) which correlated with an elevation of serum alkaline phosphatase (61.5 per cent) and bone demineralization. The mean serum phosphorus level was low and concentrations below 2.5 mg. per 100 ml. were observed in 28.3 per cent. These findings indicate malabsorption of minerals and vitamin D compatible with osteomalacia.

Hypokalemia was noted in 16.7 per cent of patients. Hypokalemia in sprue patients (potassium levels of 2.5 to 3.0 mEq. per l.) with attendant clinical symptoms of profound muscle weakness, mental apathy and personality changes has been recently stressed (4). In our series, while serum potassium levels below 3.5 mEq. per l. were seen, they occurred mostly in patients in severe relapse. However, a tendency to comparatively low potassium levels has been observed in patients in remission.

Hypoglycemia (fasting blood sugar level below 70 mg. per 100 ml.) was noted in 12.2 per cent of patients. Serum lipid levels were generally depressed, with the most marked decrease in serum total and esterified cholesterol. Mean levels of serum total and esterified cholesterol were 162 and 112 mg. per 100 ml., respectively. Serum phospholipids averaged 203 and total lipid 584 mg. per 100 ml. Low levels of serum lipids have been reported by others (11, 20, 27). Cholesterol levels below 150 mg. per 100 ml. were observed in 50.6 per cent of patients while low levels of phospholipids (below 200 mg. per 100 ml.) and total lipid (below 500 mg. per 100 ml.) were observed in 59.5 per cent and 40.5 per cent respectively. Serum levels of vitamin A and carotene were also low, with mean figures of 31.3 and 56.3 μg. per 100 ml., respectively. Despite low carotene levels, three instances of carotenemia were encountered (325, 346 and 420 μg. per 100 ml.). These three patients had normal vitamin A absorption.

The abnormalities observed in liver function were of a mild degree. Slight increase in serum bilirubin in the absence of clinical jaundice, or some impairment of bromsulphalein excretion were noted in 21.4 per cent of 42 patients examined. These findings may be correlated with the known effect of malnutrition on liver function.

ABSORPTION TESTS AND SPECIAL STUDIES

Absorption tests were carried out in the majority of patients. An oral glucose tolerance test was performed on 75 patients. In 92 per cent the curve was flat (Table III) with a mean elevation from a fasting level of 79 to a peak level of 111 mg. per 100 ml. after ingestion of 100 grams of glucose. The occurrence of a flat glucose tolerance test in sprue has been confirmed by many investigators since Thaysen's original observation (2). In six cases the oral glucose tolerance test was normal. In one patient, a known diabetic, the curve was extremely high and was not included in determining the average figures.

An oral vitamin A tolerance test was performed in 55 instances. The mean fasting level was 31.3 μg. per 100 ml. and rose to a mean peak level of 53.3 after ingestion of 180,000 units of vitamin A given as oleum percomorphum. The finding of normal absorption of vitamin A in oil in some patients with sprue could not be correlated with normal glucose absorption, nor was there any strict relation to the degree or presence of steatorrhea or of the sprue pattern of the small bowel on x-ray examination. Absorption of radioactive vitamin B_{12} given orally was studied in 23 patients (Schilling test). The mean urinary excretion was 2.9 per cent of the administered dose, compared to a normal mean excretion level of 18 per cent. Depressed excretion was found in 87 per cent of patients (Table III). There was no increase in absorption in sprue patients when intrinsic factor was added. These observations are reported in detail elsewhere (28).

Pancreatic function studies were carried out in 21 patients. A decrease in enzyme secretion was demonstrated in 14.3 per cent (Table III). This again may be related to effects of malnutrition.

Quantitative analysis of fecal fat was done in 58 patients. Steatorrhea (fecal fat above 15 per cent of dry weight) was present in 93.1 per cent. Fecal fat levels above 25 per cent were noted in 75.9 per cent of patients (Table III). The mean total fat level was 38.0 per cent of dry weight of feces. In four patients the fecal fat excretion was reported below 15 per cent of dry weight. The explanation for the low fat excretion may lie in the restricted dietary fat intake at the time of examination. The importance of this factor has been emphasized previously (7).

ROENTGEN STUDIES

Roentgen examination of the small intestine was performed in 71 patients. A sprue pattern (29–31) (dilatation, late segmentation, thickened folds, hypersecretion) was demonstrated in 87.3 per cent (Table III). X-ray changes were seen in the duodenum in 12.7 per cent of these patients; small intestinal transit time was increased in 6.3 per cent and decreased in 14.3 per cent. Studies of the colon by barium enema were obtained in about half of the patients in whom the small bowel had been examined. No abnormalities were present except for marked dilatation in cases with advanced sprue. Sigmoidoscopy, performed in 24 patients, was negative in all instances except that pallor of the mucosa was seen in a few cases.

The bones were examined roentgenologically in 37 patients. In 40.5 per cent there was no abnormality. Slight demineralization was present in 10.8 per cent: moderate or severe osteoporosis (osteomalacia) was noted in 35.2 and 13.5 per cent, respectively. Fractures were observed in 16.2 per cent and were unrelated to trauma. Ribs were involved in three patients, the femur on two occasions, and vertebrae, scapula and clavicle each in one instance. One patient was severely dwarfed. A detailed discussion of the bone abnormalities in sprue is presented elsewhere (32).

COMPLICATIONS

Complications noted in this series included intestinal obstruction in four patients. In two instances volvulus of the sigmoid occurred (both patients died). One patient had volvulus of the cecum demonstrated on exploration. In one patient peritoneal adhesions were found at operation. The occurrence of such complications has been commented on elsewhere (33). No additional cases have been added in the present series. One patient, whose course was complicated by recurrent abdominal pain and gastrointestinal hemorrhages, died and had multiple ulcerations of the small intestine (34).

Septicemia with gram-negative organisms occurred in two patients. Although low-grade fever was encountered in a small per cent of cases previously reported (7), no instances of sepsis were found. Both patients were severely ill, with other major complications including bleeding and tetany. The finding of a gram-negative organism (*E. coli* and *A. aerogenes*) suggested an origin from the bowel.

ASSOCIATED CONDITIONS

Carcinoma of the gastrointestinal tract was discovered in five patients with prolonged courses of idiopathic sprue. Three patients developed gastric carcinomas 9, 13 and 17 years after sprue was diagnosed; one had carcinoma of the esophagus 12 years later and one had a carcinoma of the ascending colon three years afterwards. In the last three instances the lesions were surgically resected. In all but two patients the symptoms of sprue were in remission when symptoms of the carcinoma became manifest. While the development of gastrointestinal malignancies in patients with long-standing, idiopathic sprue is of interest, any relationship between the two conditions is obscure. In view of the small number of these cases observed, a comparison with the established high incidence of gastric carcinoma in pernicious anemia is not warranted at the present time. It should be emphasized, however, that co-existing gastrointestinal neoplasm should be considered if suspicious symptoms develop, rather than attribute the latter entirely to the sprue syndrome.

No patients had evidence of bacterial pathogens or parasites in the stool while under observation. Three patients had a history of intestinal parasitism and two of dysentery.

Two patients had diabetes mellitus prior to hospitalization for sprue; one patient subsequently developed diabetes. The association of these two disorders is infrequent in our observation. It is necessary to rule out pancreatic dysfunction as a common etiology and to eliminate the possibility of diabetic visceral neuropathy as a cause of diarrhea and steatorrhea (8). Thompson has noted an increased incidence of diabetes in patients with celiac disease (35).

Three patients had a proven duodenal ulcer prior to hospitalization for the sprue syndrome. Eight patients had a history of syphilis and/or positive serology. Two patients had hypertension, in one this developed subsequent to steroid therapy, while the other had known hypertension for 20 years. A past history of tuberculosis was given by two patients; one had pulmonary involvement and the other cervical adenitis.

EFFECT OF MANAGEMENT ON SYMPTOMS AND SIGNS

The patients were treated with a variety of agents (24, 36–39). Two patients received only the conventional sprue diet (low-fat, high-protein, high-calorie, bland, low-residue) with multiple vitamin supplements. In 45 patients parenteral liver extract was added to the regimen. Four patients received oral folic acid in addition to liver extract. In nine patients parenteral vitamin B_{12} was administered, in addition to liver extract and folic acid. Thirty-four patients, who failed to respond adequately to diet and anti-anemic therapy were then placed on steroid therapy in addition. After an initial response was obtained the patients were maintained for long periods on minimal dosages of steroids. Initially, corticotrophin and cortisone were used, followed in turn by hydrocortisone and more recently by prednisone and prednisolone.

The response to therapy was classified according to the following categories: (a) remission; (b) full clinical control; (c) partial clinical control; (d) no change; (e) fatal termination (Table IV).

Six patients achieved complete remission, i.e., became asymptomatic without

TABLE IV

Comparison of results of conventional and steroid therapy in sprue

Management	Remission	Full Clinical Control	Partial Clinical Control	No Change	Deceased	Total
Conventional						
No.	6	20	20	4	10	60
%	10.0	33.3	33.3	6.7	16.7	
Steroid Therapy						
No.	0	20	12	1	4	34
%	0	58.8	26.5	2.9	11.8	
Total						
No.	6	40	29	5	14	94
%	6.4	42.5	30.9	5.3	14.9	

therapy. Five of these had been treated with crude liver extract and one patient with a combination of liver extract and vitamin B_{12}. Five of these patients were Puerto Rican. The non-Puerto Rican patient was asymptomatic without treatment for 10 years before her death in an old age home.

Forty patients were fully controlled with prolonged therapy. Seventeen of these patients were controlled with liver extract; one with liver extract and folic acid; two with liver extract, folic acid and vitamin B_{12}; and 20 with all three anti-anemic factors plus steroid therapy.

Improvement and partial clinical control with therapy resulted in 29 patients. One received diet and vitamins alone; 13 were given liver extract; one received liver extract with folic acid; five had liver extract, folic acid and vitamin B_{12}; and 9 were given all these agents plus steroids.

No change was observed in five patients. One received diet alone, two had liver extract, one was given liver extract and folic acid, and one received steroids.

Of the 14 patients whose death was attributable to sprue, eight were receiving liver extract; one, liver extract and folic acid; one, liver extract, folic acid and vitamin B_{12}; and four, steroid therapy in addition to the other three factors. Of the four patients who received steroids and died, one was the patient previously described with abdominal pain, gastrointestinal bleeding and ulcerations (34); the others were treated inadequately or only terminally. A more detailed discussion of the current management of sprue is presented elsewhere in this symposium (41).

Response to therapy resulted in a diminished number of bowel movements with semi-formed or formed stools. Appetite improved rapidly, followed by marked gain in weight. A feeling of well being supplanted the initial lassitude and weakness. Glossitis subsided. Macrocytic anemia responded well to specific therapy. Abdominal distention and flatulence often persisted despite cessation of diarrhea. Even under full clinical control, in many instances there was a tendency to loose bowel movements under conditions of emotional stress, intercurrent infection and dietary indiscretion. Consistent hypotension was observed in many sprue patients whose symptoms were well controlled. Rapid correction of signs of avitaminosis usually occurred and such features as cheilosis, dry skin and hemorrhagic phenomena due to hypoprothrombinemia subsided.

More resistant to correction were the objective evidences of malabsorption such as the various tests of carbohydrate and fat absorption, steatorrhea, and the sprue pattern of the small intestine. While improvement was noted, complete return to normal did not occur in the more severe forms of the disorder.

In some patients isolated selective defects persisted during periods of good clinical control, such as tetany and hypocalcemia, bone pain, factures and osteomalacia, iron deficiency anemia, subacute combined degeneration and other neurologic abnormalities, hypoproteinemia and edema.

SYMPTOMS AND SIGNS IN PUERTO RICANS VERSUS NON-PUERTO RICANS

The group of 23 patients of Puerto Rican nativity was deemed worthy of separate scrutiny. Those patients in whom the onset of symptoms occurred while in Puerto Rico could be considered to have tropical sprue. Since a disorder like sprue presents multiple symptoms, and relapses and remissions over a long period of time, it is difficult to assign the exact time at which the disease became manifest. The majority of patients reported symptoms before emigrating to the United States and could be considered as having the tropical variety of sprue. Therefore, all patients from Puerto Rico were considered separately for comparison. They provided a contrast to the 71 non-Puerto Rican patients who had developed sprue in temperate climates.

A number of differences were apparent (Table V). The mean duration of symptoms prior to hospitalization was considerably shorter in Puerto Ricans (2.3 years versus 8.8 years). There was a higher incidence of glossitis (74.1 per cent) and paresthesias (26.1 per cent) among Puerto Rican patients, while tetany (8.7 per cent) and bleeding (8.7 per cent) were less frequently observed. Differences in signs in the tropical group included a higher incidence of hepatomegaly (52.2 per cent) and splenomegaly (17.4 per cent) and a lower incidence of clubbing (8.7 per cent). Among these patients, severe anemia was encountered more frequently; 34.8 per cent had hemoglobin levels below 5 gm. per cent. In 89 per cent of examinations, the bone marrow was megaloblastic. Macrocytosis and leukopenia (74.0 per cent) were also more common in Puerto Ricans. Serum albumin levels were higher (4.0 gm. per 100 ml.). The mean serum calcium was slightly higher (8.8 mg. per 100 ml.) and a level below 7 was observed only once in 17 determinations on Puerto Rican patients as compared with an incidence of 32.4 per cent in non-Puerto Ricans. This may be correlated with the less frequent occurrence of bone demineralization among these patients (20 per cent). The only fatality in this group occurred after appendectomy, while the sprue syndrome was in remission. Response to therapy was better among Puerto

TABLE V

Comparison of clinical and laboratory data in Puerto Rican and non-Puerto Rican patients with sprue

	Non-Puerto Rican	Puerto Rican
No. of patients	71	23
Duration of symptoms	8.8 yrs.	2.3 yrs.
Glossitis	46.5%	74.0%
Bleeding	33.8%	8.7%
Tetany	29.6%	8.7%
Clubbing	26.8%	8.7%
Hepatomegaly	25.4%	52.2%
Paresthesias	15.5%	26.1%
Splenomegaly	2.8%	17.4%
Megaloblastic bone marrow	9.5%	89.0%
Hemoglobin < 5 gm.%	7.0%	34.8%
Leukopenia	24.6%	74.0%
Bone demineralization	65.6%	20.0%
Calcium < 7 mg.%	38.9%	5.9%
Mortality	18.2%	4.4%
Cured	1.7%	21.7%

Rican patients. In five patients remission was effected. In 12 patients full clinical control was induced by conventional therapy. Six patients were partially controlled, only one of whom required steroid therapy. No therapeutic failures were encountered.

These differences in symptomatology, signs and therapeutic response among Puerto Rican patients with sprue have been observed by others (5, 9, 42). An explanation may lie in the earlier recognition and treatment of these patients who present mainly with hematologic disturbances rather than more profound metabolic derangements. That sprue in Puerto Rico need not necessarily be associated with macrocytic anemia and deficiency states (glossitis) has recently been emphasized by Gardner (19) who recognized an early malabsorption syndrome without these features in military personnel in Puerto Rico.

DISCUSSION

Sprue as a Problem in Diagnosis. The diagnosis of idiopathic sprue in the typical case presents no difficulties. The physician is confronted by a middle-aged person who has had a long history of intermittent diarrhea, periods of marked and rapid weight loss, severe weakness and usually a sore mouth and tongue. There is a variety of abdominal complaints including flatulence, discomfort or nausea. Often either hemorrhagic phenomena, tetany or paresthesias are present. The patient is poorly nourished and moderately pale. Often the abdomen is distended and dependent edema may be present. The blood pressure is low. Clubbing of fingers or toes may be present. A few significant laboratory tests confirm the diagnosis. Anemia is usually present, often associated with a megaloblastic bone marrow in the absence of achlorhydria. The prothrombin time is prolonged. Serum albumin is usually below 3.5 gm. per 100 ml. and serum calcium is less than 9.0 mg. per 100 ml. along with an increase in alkaline phosphatase. All serum lipid fractions are low. The glucose and vitamin A tolerance curves are flat. There is evidence of diminished absorption of vitamin B_{12}. Steatorrhea is present along with a sprue pattern on roentgenologic examination of the small intestine. The bones are demineralized on roentgenologic examination.

Aside from such patients, there is a group of milder or incomplete clinical instances that remain diagnostic problems. Some otherwise typical patients have no diarrhea, although steatorrhea is present. In other instances, a major presenting symptom such as severe bleeding (due to hypoprothrombinemia) (43), fractures (due to osteomalacia) (17, 18), or intractable edema (due to hypoproteinemia) (44) may mask the underlying disorder which may be of a mild character. Patients are often seen who have been partially responsive to therapy and thereby resemble a *forme fruste* of the disease (7).

Comparison of old and new series. In comparing the present review with the study presented from this hospital in 1947 (7), some differences are apparent. While 36 patients with primary sprue were reported in the 15 year period from 1931 to 1946, 64 patients with long follow-up periods were seen in the 10 year period from 1946 to 1956. The increased number is probably due to greater awareness of the disease rather than an actual increase in the incidence of sprue.

The clinical features of the disease were strikingly similar in both the old and new series, including the long duration of disease prior to recognition and the major complaints. There was a lower incidence of glossitis in the present series, with an increased incidence of hemorrhagic phenomena. The physical findings compared favorably, with the exception of a decreased incidence of skin pigmentation and an increased number of neurologic abnormalities. Laboratory data were remarkably alike. The mortality was higher in the earlier review than in the present series, even though the number of patients in remission in recent years was less. This may reflect the fact that milder forms of sprue may now be suppressed by the increased availability of a better diet or earlier treatment with liver extract and vitamin B_{12}. On the other hand, more severe forms of the disorder which do not respond to such conventional therapy improve with steroids.

Complications and associated diseases in the present survey include intestinal obstruction, severe gastrointestinal hemorrhage and ulcerations, septicemia, gastrointestinal malignancies, diabetes mellitus and duodenal ulcer. Although the first complication has been recognized in the past (33), the others are newly described associated features, the significance of which is not fully apparent at present.

Tropical versus non-tropical sprue. The opportunity to make observations on tropical sprue was afforded by the inclusion of a number of patients born in Puerto Rico. While the separation is somewhat artificial, since the symptoms might have developed either in Puerto Rico or in New York, differences from the non-Puerto Rican sprue patients were observed. The typical Puerto Rican patient presented with symptoms of shorter duration. Glossitis was prominent. Paresthesias were often noted; but tetany, hemorrhagic phenomena and clubbing were rare. Hepatomegaly was usual, and splenomegaly was not infrequent. There was a high incidence of severe macrocytic anemia, leukopenia and a megaloblastic bone marrow. Very low serum calcium levels were rare and bone demineralization uncommon. Osteomalacia was seen only in 1 patient and is rarely observed in tropical sprue (5, 9). One may speculate that increased exposure to sunshine and thereby increased availability of vitamin D may be responsible.

Tropical sprue has been similarly characterized by other observers and the same differences from non-tropical sprue were apparent (5, 9, 26, 27, 42). While there is ample evidence that sprue is a single disorder, genetically transmitted and probably an inborn error of metabolism (1, 2, 4, 8, 27, 45), clinical varieties do exist. The trigger mechanism of sprue in the tropics remains to be elucidated. The impaired nutritional state with multiple dietary inadequacies and higher incidence of parasitic infestation may be important factors.

Tropical sprue has been considered a disorder curable by a single course of therapy (27). However, evidence is accumulating that asymptomatic patients may present objective signs of the metabolic disorder, such as malabsorption of carbohydrates and fats, steatorrhea and roentgenologic abnormalities of the small intestine (19). Similar observations have been made in children who have recovered from celiac disease (46) and in non-tropical sprue (31), suggesting that celiac disease, tropical and non-tropical sprue represent varying manifestations of the same basic disorder.

SUMMARY

Ninety-four patients with idiopathic sprue, including 23 patients born in Puerto Rico (tropical sprue) were studied.

The disorder was characterized by long duration of symptoms, chiefly, diarrhea, weakness, weight loss, glossitis and abdominal flatulence. Hypotension, tetany, clubbing and hemorrhagic manifestations were prominent signs. Laboratory features included megaloblastic anemia, hypoproteinemia, hypocalcemia and hypolipidemia. Malabsorption was evidenced by steatorrhea, flat glucose and vitamin A tolerance curves, and impaired absorption of radioactive B_{12}. The typical roentgenologic appearance of the small intestine was encountered.

Unusual complications included volvulus of the cecum or sigmoid and septicemia. A small number of patients developed carcinoma of the gastrointestinal tract; the significance of this observation is obscure.

The effect of various types of therapy on the course of the disease was studied. Differences in symptoms and signs and in the response to therapy were found in the Puerto Rican patients (tropical sprue).

Emphasis was placed on the diagnostic problem presented by patients with atypical or incomplete forms of the disorder.

REFERENCES

1. ADLERSBERG, D.: Problems of Management of Idiopathic Sprue. N. Y. State Jour. Med., 55: 24, 1955.
2. THAYSEN, T. E. H.: Non-tropical Sprue. A Study in Idiopathic Steatorrhea. London, Humphrey Milford, 1932.
3. HANES, F. M., AND MCBRYDE, A.: Identity of Sprue, Non-tropical Sprue and Celiac Disease. Arch. Int. Med., 58: 1, 1936.
4. COOKE, W. T., PEENEY, A. L. P., AND HAWKINS, C. F.: Symptoms, Signs and Diagnostic Features of Idiopathic Steatorrhea. Quart. J. Med., 22: 59, 1953.
5. SNELL, A. M.: Tropical and Non-tropical Sprue (Chronic Idiopathic Steatorrhea): Their Probable Inter-relationship. Ann. Int. Med., 12: 1632, 1939.
6. ADLERSBERG, D.: Ueber das Wesen und die Behandlung der Idiopathischen Sprue. Wien. Klin. Wchnschr., 67: 855, 1955.
7. ADLERSBERG, D., AND SCHEIN, J.: Clinical and Pathologic Studies in Sprue. J.A.M.A., 134: 1459, 1947.
8. COMFORT, M. W., AND WOLLAEGER, E. E.: Non-tropical Sprue Pathologic Physiology, Diagnosis and Therapy. A.M.A. Arch. Int. Med., 98: 807, 1956.
9. RODRIGUEZ-MOLINA, R.: Fundamental Concepts in the Diagnosis of Sprue. Ann. Int. Med., 40: 33, 1954.
10. DAVIDSON, L. S. P., AND FOUNTAIN, J. R.: Incidence of Sprue Syndrome with Some Observations on the Natural History. Brit. Med. Jour., 1: 1157, 1950.
11. MANSON-BAHR, P.: The Dysenteric Disorders. 2nd Ed. Williams and Wilkins Co., Baltimore, Md., 1943.
12. SUAREZ, R. M.: Clinical and Hematological Review of Sprue based on the Study of 150 Cases. Ann. Int. Med., 12: 529, 1938.

13. Hanes, F. M.: Diagnostic Criteria and Resistance to Therapy in the Sprue Syndrome. Am. J. Med. Sci., 204: 436, 1942.
14. Hanes, F. M.: Sprue in Oxford Medicine, 5: 631, 1943.
15. Keele, K. D.: A Study of the Onset and Cyclic Development of the Sprue Syndrome. Brit. Med. Jour., 2: 111, 1946.
16. Himes, H. W., and Adlesberg, D.: Pathologic Studies in Idiopathic Sprue. This volume, page 77.
17. Cameron, D. G., Bensley, E. H., and Wood, P.: Latent Steatorrhea. Ann. Int. Med., 37: 553, 1952.
18. Juergens, J. L., Scholz, D. A., and Wollaeger, E. E.: Severe Osteomalacia associated with Occult Steatorrhea Due to Non-tropical Sprue. AMA Arch. Int. Med., 98: 774, 1956.
19. Gardner, F. H.: A Malabsorption Syndrome in Military Personnel in Puerto Rico. A.M.A. Arch. Int. Med., 98: 44, 1956.
20. Thaysen, T. E. H.: Ten Cases of Idiopathic Steatorrhea. Quart. J. Med., 4: 359, 1935.
21. Wang, C. I., and Bossak, E. T.: Hemorrhagic Manifestations in Idiopathic Sprue: A Report of 25 Cases and Review of the Literature. This volume, page 143.
22. Goolker, P., and Schein, J.: Psychic Effects of ACTH and Cortisone. Psychosomatic Med., 15: 389, 1953.
23. Sencer, W.: Neurological Manifestations in the Malabsorption Syndrome. This volume, page 157.
24. Castle, W. B., Rhoads, C. P., Lawson, H. A., and Payne, G. I.: Etiology and Treatment of Sprue: Observations in Patients in Puerto Rico and Subsequent Experiments in Animals. Arch. Int. Med., 56: 627, 1935.
25. Badenoch, J., and Callender, S. T.: Iron Metabolism in Steatorrhea: The Use of Radioactive Iron in Studies of Absorption and Utilization. Blood, 9: 123, 1954.
26. Stefanini, M.: Clinical Features and Pathogenesis of Tropical Sprue. Medicine, 27: 379, 1948.
27. Frazer, A. C.: Fat Metabolism and the Sprue Syndrome. Brit. Med. Jour., 2: 769, 1949.
28. Oxenhorn, S., Estren, S., and Adlersberg, D.: Intestinal Uptake of Vitamin B_{12} in the Malabsorption Syndrome. This volume, page 58.
29. Snell, A. M., and Camp, J. D.: Chronic Idiopathic Steatorrhea: Roentgenologic Observations. Arch. Int. Med., 53: 615, 1934.
30. Kantor, J. L.: The Roentgen Diagnosis of Idiopathic Steatorrhea and Allied Conditions. Am. J. Roent., 41: 758, 1939.
31. Adlersberg, D., Marshak, R. H., Colcher, H., Drachman, S. R., Friedman, A. I., and Wang, C. I.: The Roentgenologic Appearance of the Small Intestine in Sprue. Gastroenterology, 26: 548, 1954.
32. Hartley, J.: Osseous Changes and Fractures in Malabsorption Syndrome. This volume, page 172.
33. Glazer, I., and Adlersberg, D.: Volvulus of the Colon: A Complication of Sprue. Gastroenterology, 24: 159, 1953.
34. Himes, H. W., Gabriel, J. B., and Adlersberg, D.: Previously Undescribed Clinical and Post-mortem Observations in Non-tropical Sprue: Possible Role of Prolonged Corticosteroid Therapy. Gastroenterology, 32: 60, 1957.
35. Thompson, M. W.: Heredity, Maternal Age, Birth Order in Etiology of Celiac Disease. Am. J. Human Genetics, 3: 159, 1951.
36. Rhoads, C. P., and Miller, D. K.: Intensive Liver Extract Therapy of Sprue. J.A.M.A., 103: 387, 1934.
37. Spies, T. D., Milanes, F., Menendez, A., Koch, M. B., and Minnich, V.: Observa-

tions in the Treatment of Tropical Sprue with Folic Acid. J. Lab. & Clin. Med., 31: 227, 1946.

38. Spies, T. D., Suarez, R. M., Garcia-Lopez, G., Milanes, F., Stone, R. E., Lopez-Toca, R., Aramburu, T., and Karbus, S.: Tentative Appraisal of Vitamin B_{12} as a Therapeutic Agent. J.A.M.A., 139: 521, 1949.
39. Taylor, A. B., Wollaeger, E. E., Comfort, M. W., and Power, M. H.: The Effect of Cortisone on Nontropical Sprue. Gastroenterology, 20: 203, 1952.
40. Adlersberg, D., Cilcher, H., and Wang, C. I.: Oral Use of Hydrocortisone (Compound F) in Treatment of Sprue. A.M.A. Arch. Int. Med., 92: 615, 1953.
41. Colcher, H., and Adlersberg, D.: Management of Patients with Malabsorption Syndrome. This volume, page 206.
42. Patterson, J. C. S.: The Sprue Syndrome. Am. J. Med. Sci., 231: 92, 1956.
43. Ingelfinger, F.: The Diagnosis of Sprue in Nontropical Areas. New Eng. J. Med., 228: 180, 1943.
44. Adlersberg, D., Wang, C. I., and Bossak, E. T.: Disturbances in Protein and Lipid Metabolism in Malabsorption Syndrome. This volume, page 32.
45. Bennett, T. I., Hunter, D., and Vaughan, J. M.: Idiopathic Steatorrhea (Gee's Disease). Quart. J. Med., 1: 603, 1932.
46. Andersen, D. H., and Di Sant'Agnese, P. A.: Idiopathic Celiac Disease. Pediatrics, 11: 207, 1953.

THE BLOOD AND BONE MARROW IN IDIOPATHIC SPRUE

SOLOMON ESTREN, M.D.
New York, N. Y.

Anemia is a characteristic accompaniment of the malabsorption syndromes. So regular is the occurrence of anemia in the primary sprues that, in the words of Cooke and co-workers, "we have come to regard persistently normal blood values as a strong evidence against the diagnosis" (1). Sooner or later, most or all untreated patients with sprue show anemia (2), although at any given time—for example, at the time of initial medical examination—the incidence of anemia varies according to differences in the severity of the disease (3). It is the purpose of this report to review the hematologic disturbances in primary sprue, and to discuss their significance and pathogenesis in the light of current concepts and modern technics of study.

DEFINITIONS

Celiac disease, tropical sprue and non-tropical sprue are now generally considered different manifestations of the same basic pathophysiologic disturbance (1). The terms "sprue" and "malabsorption syndrome" may properly be applied to all three. Thaysen's term "idiopathic steatorrhea" includes all three disorders (4), but some British workers (5) restrict the identical phrase—idiopathic steatorrhea—to only celiac disease and non-tropical sprue, considering that tropical sprue is a different disorder. We shall use the terms "sprue," "malabsorption syndrome," and "idiopathic steatorrhea" interchangeably to include all three forms of the disturbance, but shall specify (for hematologic reasons which will become apparent shortly) "celiac disease" when that entity is under discussion.

MATERIALS

Included in this report are studies on 94 patients with idiopathic sprue. The diagnosis was established following clinical and laboratory studies which included gastrointestinal x-rays, stool examinations for fat, glucose and vitamin A tolerance tests, pancreatic studies and hematologic studies. The details of these patients are presented in another paper in the present symposium (6). Initial hematologic studies were tabulated and analyzed, and the results are summarized in Table I. Studies of intestinal absorption of vitamin B_{12} were made in 25 of the patients and are discussed elsewhere (7). The results of these hematologic studies are also listed in Tables II, IV, V, and VI.

THE ANEMIA

In 1928, Carmichael-Low found macrocytosis "as a general rule" in all of 150 cases of tropical sprue, and macrocytic anemia in 60 per cent (8). In 1929, Serra

From the Department of Hematology, The Mount Sinai Hospital, New York City.

These studies were supported in part by the Albert A. List, Frederick Machlin, and Anne Ruth Lowenberg Research Funds; and by grants from Squibb Institute for Medical Research, New Brunswick, New Jersey, and Merck and Company, Rahway, New Jersey

TABLE I

Hematology of Author's Cases of Idiopathic Sprue

	Number of Cases	Mean	Range
Hemoglobin gm./100 ml.	94	9.3	2.4–15.5
Red Cells millions/cu. mm.	83	3.11	0.66–5.7
Hematocrit %	29	33.5	12–46
White Cells per cu. mm.	83	5,900	1,700–13,800
Polymorphonuclear Leukocytes per cu. mm.	83	4,600	1,050–12,600
Lymphocytes per cu. mm.	83	2,000	600–5,900
Platelets per cu. mm.	54	195,000	30,000–520,000
Sedimentation Rate (Westergren) mm. in 1 hour	32	29	3–104
Prothrombin Time (one-stage) seconds	37	19.5 (control, 12.7)	10.5–51

reported macrocytic anemia in 89 per cent of 45 cases of tropical sprue (9). In 1930, Manson-Bahr and Willoughby, in describing 200 cases of tropical sprue, again reported macrocytosis for the entire series, and macrocytic anemia in 46 per cent (10).

This pattern of observation has continued (11–22), so that studies of over 2,400 cases of tropical sprue, non-tropical sprue, and idiopathic steatorrhea throughout the world have established the general rule that the characteristic erythropoietic disturbance in the malabsorption syndrome is the development of macrocytosis, due to megaloblastic erythropoiesis in the bone marrow. When the patient is sufficiently sick, macrocytosis is superseded by macrocytic, megaloblastic anemia (Table II).

In the mildest cases, and when treatment is adequate, there is no anemia, but macrocytosis may still be present (19). In less early cases, macrocytosis without anemia may still be seen (16, 17, 19); or, alternatively, normocytic (23) or normocytic hypochromic (3, 21) anemia may occasionally be noted. As the disorder progresses, the anemia becomes more severe and frankly macrocytic, with a megaloblastic marrow (3, 14). Superficially, this severe macrocytic anemia resembles pernicious anemia (see below).

Macrocytosis is reported in 50 to 100 per cent of cases of sprue sufficiently symptomatic to visit the physician. According to Cooke and co-workers (1), two-thirds of patients with sprue show macrocytosis when first seen, and all such patients show macrocytosis sooner or later under continued observation. Macrocytic *anemia* is reported in from 14 to 95 per cent of untreated cases of sprue (3, 16, 17, 22).

In occasional cases, the anemia of sprue is hypochromic (14, 17, 21, 24, 25, 26). The incidence varies from 6 to 17 per cent of unselected uncomplicated cases. In celiac disease, as opposed to the other forms of the malabsorption syndrome, the anemia, when it is present, is regularly hypochromic (21).

In rare cases, aplastic anemia has been reported (3). The "hemolytic anemia" described in the older literature (8) has not been substantiated.

Among the author's 94 cases of idiopathic sprue, macrocytosis was found in 57.6 per cent, while 33 per cent were normocytic, and 9.4 per cent hypochromic at the time of initial observation (Table I). The type of anemia sometimes changed during prolonged observation. Thus, in 6 of the author's cases, macrocytosis was present on some occasions, and normocytosis in others. In 3 cases, hypochromia was present on some occasions, and normochromia and normocytosis on others. One patient's anemia was macrocytic, normocytic, and hypochromic at different times in her course.

In these 94 patients, the mean hemoglobin was 9.3 grams, and anemia of 10 grams or less occurred in 51 per cent of the cases. The mean red cell count was 3,110,000; 55 per cent of the patients had less than 3,500,000 red cells when first observed. These findings agree substantially with those in the literature.

TABLE II

Reports of the Blood Picture in Sprue

Reference	No. Cases	Diagnosis	Location	Blood Picture
Carmichael-Low (8)	150	Tropical Sprue	England	Macrocytosis in practically all Macrocytic anemia in 60%
Serra (9)	45	Tropical Sprue	Puerto Rico	Macrocytic anemia in 89%
Fairley (11)	63	Tropical Sprue	India	Macrocytosis in over 50%
Baumgartner (12)	36	"Sprue"	N. Y. State	Macrocytic anemia in 45%
Manson-Bahr (10)	200	Tropical Sprue	England	Macrocytosis in all Macrocytic anemia in 46%
Suarez (13)	70	Tropical Sprue	Porto Rico	Macrocytic anemia in 91%
Castle (14)	92	Tropical Sprue	Porto Rico	Macrocytic anemia in 94% Hypochromic anemia in 6% (selected cases)
Thaysen (4)	45	Non-tropical Sprue	Denmark	"Hyperchromic" anemia in 66%
Suarez (15)	150	Tropical Sprue	Porto Rico	Macrocytosis in 99%
Rodriguez-Molina (16)	100	Tropical Sprue	Porto Rico	Macrocytosis in 90% Hypochromia in 17%
Keele (17)	80	Tropical Sprue	British in India	Macrocytosis in 56% Macrocytic anemia in 26% Hypochromic anemia in 9%
Adlersberg (18)	36	Idiopathic Sprue	N. Y. City	Macrocytic anemia in 53%
Stefanini (3)	1069	Tropical Sprue	Italians in India	Macrocytic anemia in 14% Aplastic anemia in 0.3%
Innes (19)	17	Tropical Sprue	Scotland	Macrocytosis in 80%
	27	Non-tropical Sprue		Macrocytosis in 67% Hypochromia in 15%
Cooke (20)	33	Idiopathic Steatorrhea	England	Color index high in 66%
Lopez (52)	155	Tropical Sprue	Cuba	Macrocytic anemia in 100% (selected cases)
Present report	94	Idiopathic Sprue	N. Y. City	Macrocytic anemia in 58% Hypochromic anemia in 9%

SPRUE VS. PERNICIOUS ANEMIA

In the older literature, the fact that macrocytosis and megaloblastic erythropoiesis occurred both in pernicious anemia and in the malabsorption states led a number of workers to report that the peripheral blood in the two conditions is identical (16). However, it was early established that the two disorders were not the same (9, 14). It is only in certain very severe cases that the anisocytosis, poikilocytosis, leukopenia, thrombocytopenia and normoblastosis which occur in pernicious anemia are found in sprue (3). The hematologic resemblance between the two disorders results from the same basic process: malabsorption of erythropoietic substances from the diet. However, the reasons for the malabsorption are different, and the blood picture in sprue may be distinguished from that in pernicious anemia by a number of features (Table III):

TABLE III

Pernicious Anemia vs Sprue Anemia

	Pernicious Anemia	Sprue
Type of Anemia	Macrocytic	Usually macrocytic—rarely, hypochromic
Pancytopenia	Common	Rare
Blood smear	Anisocytosis and poikilocytosis regularly present	Anisocytosis and poikilocytosis uncommonly found
Bone marrow	Megaloblastic	Sometimes megaloblastic Often "intermediate"
Gastric Juice	Achlorhydria always	Achlorhydria uncommon
Neurologic Symptoms	Common	Rare
Serum B_{12}	Very low	Low in some; normal in some
Intestinal absorption of vitamin B_{12}	Always impaired Improved by intrinsic factor	Usually impaired No effect from intrinsic factor

TABLE IV

Incidence of Hypochromic Anemia in Non-Celiac Sprue

Reference	No. Cases	Diagnosis	Location	Incidence of Hypochromic Anemia
Castle (14)	92	Tropical Sprue	Porto Rico	6%
Rodriguez-Molina (16)	100	Tropical Sprue	Porto Rico	17%
Keele (17)	80	Tropical Sprue	British in India	9%
Innes (19)	44	Tropical and Non-tropical Sprue	Scotland	0%
Stefanini (3)	1069	Tropical Sprue	Italians in India	0%
Hawkins (26)	200	Steatorrhea	England	6.5%
Present report	94	Idiopathic Sprue	N. Y. City	9%

1. In pernicious anemia, the blood smear shows not only macrocytosis, but marked variation in size and shape of the red cells. In the macrocytic anemia of sprue, poikilocytosis and anisocytosis are not prominent, and may be absent (9, 20).

2. In pernicious anemia, the bone marrow is frankly megaloblastic. In sprue with macrocytic anemia, the bone marrow may also be megaloblastic (3, 14), but in many cases it is rather "intermediate" or "transitional" in character (1, 18, 19, 27).

3. In pernicious anemia, achylia is the rule. In sprue, most cases show free gastric hydrochloric acid, and many with initial achlorhydria have a return of free acid under therapy.

4. In pernicious anemia, neurologic symptoms occur in 80 per cent of cases, and posterolateral sclerosis occurs in up to 70 per cent (28). In sprue, neurologic findings are present in less than 2 per cent, and posterolateral sclerosis is a rarity (29).

5. In pernicious anemia in relapse, the serum level of vitamin B_{12} is always low. In sprue with macrocytic anemia, two types of cases may be distinguished: those with low serum B_{12}, and those in which the serum B_{12} is normal (30, 31).

6. In pernicious anemia, the absorption of orally administered vitamin B_{12} is always impaired, both in relapse and in remission; and absorption is improved by a potent source of intrinsic factor. In sprue, the intestinal absorption of vitamin B_{12} is usually, but not invariably, impaired; intrinsic factor does not enhance absorption.

Sprue is therefore to be considered in the differential diagnosis of any patient who presents with what seems to be Addisonian pernicious anemia, and the two disorders can be distinguished with the aid of the new methods of study of vitamin B_{12}. When such studies are made in groups of patients who for years have borne the diagnosis "pernicious anemia," a few patients will often be found in whom the diagnosis is rather sprue.

HYPOCHROMIC ANEMIA IN SPRUE

In contrast to all other varieties of idiopathic sprue, whose typical hematologic abnormality is a megaloblastic, macrocytic anemia, celiac disease characteristically shows a hypochromic, microcytic anemia (19, 21, 34, 35). This is an iron-deficiency anemia, and is often refractory to treatment with oral iron preparations—i.e., there is impaired absorption of iron in the gastrointestinal tract.

A similar iron-deficiency anemia is occasionally seen in the non-celiac varieties of idiopathic sprue, instead of the usual macrocytic anemia (14, 16, 17, 19, 24, 25). In the present series, iron-deficiency was found in 9 per cent of the cases. Sometimes, there is a combination of macrocytosis and hypochromia; sometimes, there is only hypochromia; rarely, both hypochromia and microcytosis are present. This iron-deficiency anemia is notoriously refractory to treatment with oral iron (5, 24, 26) and may require parenteral iron therapy for relief (26). The sternal marrow in such cases shows normoblastic hyperplasia with or without some "intermediate" erythropoiesis (26); it is never frankly megaloblastic.

TABLE V

The Bone Marrow In Non-Celiac Sprue

Reference	No. Cases	Megaloblastic	"Intermediate"	Normal	Other
Krjukoff* (36)	16	16	—	—	—
Rhoads* (37)	22	22	—	—	—
Adlersberg (18)	12	4	5	2	1 "fatty"
Innes (19)	18	6	7	5	—
Stefanini** (3)	25	22	—	3	5 "aplastic"
Lopez (17)	155	155	—	—	—
Cooke (1)	49	17	21	11	—
Friedlander (38)	12	7	—	—	5 not stated
Gardner (39)	19	19	—	—	—
Present Report	27	10	6	10	1 "fatty"

* Surgical sections; others were marrow aspirations.

** More than one marrow study in some cases.

THE BONE MARROW IN SPRUE

When macrocytic anemia is present in a patient with sprue, the bone marrow is "megaloblastic" (Table V). As the patient goes into remission, erythropoiesis becomes normoblastic, and the marrow tends to return to normal. It is notable that the "megaloblastic" bone marrow in sprue is often not identical with that in pernicious anemia, but that the erythropoiesis is best described as "intermediate"—i.e., the red cell precursors show features of both megaloblastic and normoblastic maturation. Such "intermediate" or "transitional" erythropoiesis has subtle morphologic features which distinguish it from both normoblastic and frankly megaloblastic erythropoiesis (27). The presence of such features in a patient with supposed or atypical pernicious anemia should lead to a search for some other diagnosis, such as malabsorption syndrome.

The marrow findings in sprue are summarized in Table V. In the author's series, 27 marrow aspirations were done, of which 10 were megaloblastic, 6 "intermediate", 10 normal, and 1 fatty. Giant myelocytes and metamyelocytes were occasionally noted. In patients with sprue who are incompletely remitted, the blood shows macrocytosis without anemia, and the marrow shows "intermediate" erythropoiesis (19). Marrow aplasia has rarely been reported in sprue (3). Aplasia has not been noted in the present series.

THE OTHER BLOOD FINDINGS IN SPRUE

The white blood cell count in sprue is not remarkable, although leukopenia due to granulocytopenia has been reported in from 2 to 68 per cent of cases (Table VI). Leukocytosis occurs in less than 10 per cent of cases. In the present series, the mean white cell count was 5,900, and 31 per cent of the patients showed a white count of less than 5,000 per cu.mm. The mean granulocyte count was 4,600 per cu.mm.; 27.5 per cent of the patients showed a granulocyte count of less than 3,000 per cu.mm. The mean lymphocyte count was 2,000—i.e., lymphocytosis was only relative, not absolute. A lymphocyte count of over 4,000 per

TABLE VI

The Leukocyte Count in Sprue

Reference	No. Cases	Normal White Count	Leukopenia	Leukocytosis
Carmichael-Low (8)	114	85%	8%	7%
Manson-Bahr (10)	198	93%	2.5%	4.5%
Rodriguez-Molina (16)	99	44%	56%	0%
Stefanini (3)	153	32%	68%	0%
Innes (19)	43	79%	14%	7%
Present Report	83	63%	31%	6%

cu.mm. was present in only 4 of 83 cases (4.8 per cent). Overall leukocytosis occurred in only 5 cases (6.1 per cent), including two who showed absolute lymphocytosis. These findings are in general agreement with those in the literature. In the majority of cases of sprue (61 per cent in this series), the white blood count is normal, and the differential count unremarkable.

Qualitative changes in the leukocytes, similar to those seen in pernicious anemia, may be present in sprue. Rodriguez-Molina (16) noted giant band cells in a few cases and macrocytosis of the leukocytosis in general. Hyperlobulation of the neutrophils was noted in occasional cases (9, 16). These changes are much less frequent than in pernicious anemia. They were present in only one of the author's patients.

The platelets are usually normal (3, 16, 18). Of 54 cases examined in this series 8 (15 per cent) showed platelet counts below 100,000 per cu.mm. (direct method). There were no associated clinical findings of thrombocytopenia.

Nucleated red cells are only occasionally seen in the peripheral blood (9, 16), typically when the anemia is severe (red cells under 2 million per cu.mm.). They were noted in 7 cases of the author's series (7.5 per cent): 6 showed normoblasts, and one showed megaloblasts.

The hypotonic fragility of the red cells was found to be decreased by some workers (20), but most noted it to be normal (3, 9).

The sedimentation rate was tested by the Westergren method in 32 patients. The mean was 29.3 mm. in one hour; 18 results (56 per cent) were less than 20 mm.; and 23 (72 per cent) were less than 30 mm. in one hour. Nine patients (28 per cent) showed sedimentation rates over 30 mm.

Prothrombin time was estimated by the one-stage method in 37 patients, of whom 26 (70 per cent) showed a prothrombin time which was more than 3 seconds greater than that of the control. The mean prothrombin time was 19.5 seconds; the mean normal 12.7 seconds. Hypoprothrombinemia is discussed in a separate paper in this symposium (40), and the entire problem of hemorrhage in sprue is reviewed by Cooke (1) and others (41).

GASTRIC ACIDITY

Free hydrochloric acid is the rule in the malabsorption syndromes, although hypochlorhydria is often present. Histamine-fast achlorhydria occurs in from 1 to 15 per cent of patients with primary sprue (3, 9, 20, 39, 42). In the present series, 8 of 61 patients examined lacked free acid, even after histamine (13 per cent). In many cases of sprue with achlorhydria, free acid returns after successful therapy (42).

GASTRIC CYTOLOGY

Patients with untreated tropical sprue showed changes in squamous epithelial and the columnar cells of the stomach which were similar to those described in pernicious anemia (39). Treatment, however, was slowly followed by return of the gastric epithelium towards normal—a change which does not occur in pernicious anemia.

PATHOGENETIC STUDIES OF THE ANEMIAS OF SPRUE

The resemblance between the usual macrocytic anemia of sprue and the macrocytic anemia of pernicious anemia is the result of the megaloblastic erythropoiesis which is common to both disorders. Megaloblastic erythropoiesis results when certain essential factors are lacking at the marrow, notably vitamin B_{12} and folic acid. In pernicious anemia, it has been established that the deficiency is that of vitamin B_{12}, which cannot properly be absorbed by the patient with pernicious anemia because he lacks "intrinsic factor." In the sprue syndrome, intrinsic factor is irrelevant but malabsorption of vitamin B_{12}, folic acid and perhaps other materials is responsible for disturbed erythropoiesis at the marrow.

In 1935, Thaysen suggested that the "hyperchromic" anemia in sprue might be due to deficient absorption of an extrinsic factor present in the diet (4). Castle and Rhoads (14) suggested that, at least in most cases of sprue, the nature of the absorptive difficulty differed from that in pernicious anemia. More recently, the response of some cases of sprue to folic acid but not to vitamin B_{12} (43, 44, 45, 50), and of others to vitamin B_{12} but not to folic acid (31), has suggested that the absorptive defect might be different in different cases of sprue itself. Furthermore, it has been recognized that changes in the intestinal mucosa might be caused by dietary deficiency itself (46), which might in turn lead to malabsorption of dietary materials—a self-perpetuating cycle.

Cases of sprue show many absorptive defects (vitamin B_{12}, folic acid, fat, vitamin A, glucose, etc.). It seems likely that these difficulties in absorption are manifestations of metabolic abnormalities of various enzymes in the intestinal mucosa. The occurrence of sprue in families, and the past history of celiac disease in patients with sprue, suggest that the basic disturbance in sprue is somehow genetically transmitted. Of the multiple absorptive difficulties in sprue, those of especial hematologic interest have to do with vitamin B_{12}, folic acid, proteins and iron.

Vitamin B_{12}. Cases of sprue may be divided into those whose serum levels of vitamin B_{12}, during relapse, are low; and those in which it is normal (31, 50). Correspondingly, malabsorption of vitamin B_{12} from the intestinal tract is found in some, but not all, cases of idiopathic sprue (33, 47, 48, 49). The low serum B_{12}, when present, is a reflection of depleted tissue (marrow) stores of vitamin B_{12}. There is no apparent difficulty of utilization of B_{12}; when sprue patients with low serum B_{12} levels receive B_{12} parenterally, they regularly show hematologic response (31). This is in contrast to patients with untreated sprue whose serum B_{12} is normal; they do not respond to B_{12} therapy, but require folic acid for remission (31).

Twenty-five of the present series of cases were studied with regard to their ability to absorb vitamin B_{12} from the intestinal tract (7). Twenty patients (80 per cent) showed impaired absorption of B_{12}; in five patients (20 per cent), the absorption was normal. This impairment of B_{12} absorption is not dependent upon or improved by intrinsic factor (7, 32, 33, 48, 49)—i.e., the defect differs from that seen in pernicious anemia. However, as in pernicious anemia, it was found, in the present series of cases, that the inability to absorb orally administered vitamin B_{12} does not disappear when the patient with sprue is in remission (7).

Folic acid. Malabsorption of folic acid from the intestinal tract was found in all 8 patients with the sprue syndrome studied by Girdwood (51). No such abnormality was found in 15 cases of pernicious anemia, in 4 cases of anemia of pregnancy with megaloblastic or transitional marrow, or in 14 control individuals.

Proteins and other factors. Hypoproteinemia is a frequent finding in the sprue syndrome (52). This may be a reflection of poor absorption of dietary protein from the intestinal tract, or perhaps impaired synthesis of protein from its precursors in the body. Since proteins are necessary for normal erythropoiesis, deficient absorption and synthesis of proteins may well be factors in the impaired production of blood elements in sprue.

Owren (53) has described a "liver protein synthesis factor" which was necessary to relieve macrocytosis and hypoprothrombinemia in patients with idiopathic steatorrhea and pernicious anemia, whereas B_{12} and folic acid failed to cause remission of these features. Malabsorption of this postulated factor is assumed. Others have described other such factors, present only in crude liver extracts (54, 55).

The defect in fat absorption in sprue leads to malabsorption of vitamin K precursors, with resultant hypoprothrombinemia. In some cases, the hypoprothrombinemia seems to be due to other mechanisms, such as folic acid deficiency itself (56).

Iron. In a small proportion of patients with the malabsorption syndrome, the anemia which develops is iron-deficient. Studies have suggested, however, that perhaps all patients with idiopathic steatorrhea have a defect in the absorption of iron from the intestinal tract (24). It is not known whether this is part of a general failure of absorption, or is due to a deficiency in apoferritin in the intestinal mucosa. In addition, however, it seems probable that there is excessive loss of iron in some cases.

Pathogenesis of the Anemias of Idiopathic Sprue

Normal hematopoiesis depends, among other things, on the presence of normal amounts of vitamin B_{12}, folic acid, protein precursors and iron at the bone marrow. Deficiency of folic acid or of vitamin B_{12} at the sites of blood cell formation results in abnormal "megaloblastic" erythropoiesis, with resultant macrocytic anemia. In idiopathic sprue, defective absorption of many substances is present, including vitamin B_{12} and folic acid. In some cases, it is primarily malabsorption of dietary vitamin B_{12} which leads to the hematologic picture; in others, apparently, malabsorption of folic acid is the more important feature.

In most cases of sprue, however, it is presumably defective intestinal absorption of multiple dietary constituents—proteins, vitamin B_{12}, folic acid, other substances—which gives rise to the resultant picture in the blood: macrocytic, megaloblastic anemia.

It is of great interest that the inability of the intestinal tract to absorb vitamin B_{12} and folic acid persists whether the patient is in remission or in relapse (7, 51). This is in contrast to the situation in certain patients with secondary sprue, notably patients with intestinal blind loops and stasis, in whom impaired vitamin B_{12} absorption disappears when successful treatment with antibiotics is undertaken (57, and unpublished personal observations). In idiopathic sprue, then, as in pernicious anemia, the patient with idiopathic sprue always has the potential of developing megaloblastosis and macrocytic anemia, unless treatment is undertaken to ensure adequate supplies of malabsorbed materials to the bone marrow and other tissues.

Since there is also deficient absorption of iron from the gastrointestinal tract in some, if not all, patients with idiopathic sprue, there is a potentiality of developing iron-deficiency anemia. In actual fact, only a small percentage of sprue patients develop an anemia which is iron-deficient, and factors other than malabsorption (notably, loss of iron) may be responsible for the fulfillment of the potential of iron-deficiency. Utilization of iron is normal in such patients, and the use of parenteral iron, circumventing the intestinal defect, allows remission. The inability to absorb iron normally has been suggested to be the factor which is responsible for the occurrence of "intermediate" rather than frankly megaloblastic erythropoiesis in the macrocytic anemia of sprue (27).

SUMMARY

The changes in the blood and the bone marrow in idiopathic sprue have been discussed. Celiac disease is accompanied by an iron-deficiency anemia. Adult forms of the malabsorption syndrome—idiopathic sprue, idiopathic steatorrhea, tropical sprue—are accompanied by macrocytosis in almost all cases, and by various degrees of macrocytic anemia in cases of varying severity.

There are multiple intestinal defects of absorption in idiopathic sprue. Those of importance in the development of the hematologic picture include malabsorption of dietary protein, folic acid, vitamin B_{12} and iron. Replacement of the

deficient materials at the centers of blood formation is necessary for remission of the hematologic abnormalities.

ACKNOWLEDGMENT

The author gratefully acknowledges the encouragement and advice of Dr. David Adlersberg, who made available the patients who form the basis for this report. Special hematological studies were done under the guidance of Dr. Louis R. Wasserman, Director of the Department of Hematology.

REFERENCES

1. Cooke, W. T., Peeney, A. L. P., and Hawkins, C. F.: Symptoms, Signs, and Diagnostic Features of Idiopathic Steatorrhoea. Quart. J. Med. 22: 60, 1953.
2. Rodriguez-Molina, R.: Sprue in Puerto Rico. A Clinical Study of 100 Cases. Puerto Rico J. Pub. H. and Tr. Med. 17: 134, 1941.
3. Stefanini, M.: Clinical Features and Pathogenesis of Tropical Sprue. Observations on a Series of Cases among Italian Prisoners of War in India. Medicine 27: 379, 1948.
4. Thaysen, T. E. H.: Ten Cases of Steatorrhoea. Quart. J. Med. 4: 359, 1935.
5. Bennett, T. I., Hunter, D., and Vaughan, J. M.: Idiopathic Steatorrhoea (Gee's Disease). A Nutritional Disturbance Associated with Tetany, Osteomalacia, and Anaemia. Quart. J. Med. 1: 603, 1932.
6. Bossak, E. T., Wang, C. I., and Adlersberg, D.: Clinical Aspects of Malabsorption Syndrome (Idiopathic Sprue). This volume, page 112.
7. Oxenhorn, S., Estren, S., and Adlersberg, D.: Intestinal Uptake of Vitamin B_{12} in the Malabsorption Syndrome. This volume, page 58.
8. Carmichael-Low, G.: Sprue. An Analytical Study of 150 Cases. Quart. J. Med. 21: 523, 1928.
9. Serra, A.: The Relation of Sprue to Pernicious Anemia with a Report on Blood Changes in 45 Cases of Sprue. Am. J. Tr. Med. 9: 49, 1929.
10. Manson-Bahr, P., and Willoughby, H.: Studies on Sprue with Reference to Treatment. Quart. J. Med. 23: 411, 1930.
11. Fairley, N. H., and Jasudasoon, F.: Investigation of Value of Complement Reaction in Sprue utilizing Monilia psilosis (Ashfordi) as Antigen. Indian J. Med. Res. 16: 861, 1929.
12. Baumgartner, E. A.: The Blood Picture in Tropical Sprue. Folia Haemat. 43: 192, 1931.
13. Suarez, J.: Pernicious Anemia and Sprue. Porto Rican J. Pub. H. and Tr. Med. 7: 145, 1931.
14. Castle, W. B., Rhoads, C. P., Lawson, H. A., and Payne, G. C.: Etiology and Treatment of Sprue. Observations on Patients in Puerto Rico and Subsequent Experiments on Animals. Arch. Int. Med. 56: 627, 1935.
15. Suarez, R. M.: Clinical and Hematological Review of Sprue Based on the Study of 150 Cases. Ann. Int. Med. 12: 529, 1938.
16. Rodriguez-Molina, R.: Hematology of Sprue. Report on 100 Cases in Puerto Rico. Puerto Rico J. Pub. H. and Tr. Med. 15: 89, 1939.
17. Keele, K. D.: A Study of the Onset and Cyclic Development of the Sprue Syndrome. Brit. Med. J. 2: 111, 1946.
18. Adlersberg, D., and Schein, J.: Clinical and Pathological Studies in Sprue. J. A. M. A. 134: 1459, 1947.
19. Innes, E. M.: The Blood and Bone Marrow in the Sprue Syndrome. A Study of 63 Cases. Edinburgh Med. J. 55: 282, 1948.
20. Cooke W. T., Frazer, A. C., Peeney, A. L. P., Sammons, H. G., and Thompson,

M. D.: Anomalies of Intestinal Absorption of Fat. II. The Haematology of Idiopathic Steatorrhea. Quart. J. Med., 17: 9, 1948.

21. PATERSON, J. C. S.: The Sprue Syndrome. Am. J. Med. Sc. 231: 92, 1956.
22. RICE, M. E.: A Physiological Interpretation of the Clinical Changes in Sprue. J. Bowman-Gray School Med. 1: 144, 1943.
23. VEDDER, E. B.: A Discussion of the Etiology of Sprue. Am. J. Tr. Med. 20: 345–357, 1940.
24. BADENOCH, J., AND CALLENDER, S. T.: Iron Metabolism in Steatorrhea. The Use of Radioactive Iron in Studies of Absorption and Utilization. Blood 9: 123, 1954.
25. BARTLEY, C. W.: Steatorrhoea in a Family. Brit. M. J. 1: 1161, 1950.
26. HAWKINS, C. F., PEENEY, A. L. P., AND COOKE, W. T.: Refractory Hypochromic Anaemia and Steatorrhoea: Treatment with Intravenous Iron. Lancet 2: 387, 1950.
27. FUDENBERG, H., AND ESTREN, S.: Pernicious Anemia II. The Significance of Intermediate Megaloblastic Erythropoiesis in the Diagnosis of Pernicious and Related Anemias. In preparation.
28. SLEPIAN, A., AND VAUGHAN, S. L.: Nervous System Manifestations in Pernicious Anemia. Results of Treatment with Liver Preparations as Compared with B_{12} Therapy. N. Y. State J. Med. 51: 1524, 1951.
29. WOLTMANN, H. W., AND HECK, F. J.: Funicular Degeneration of the Spinal Cord without Pernicious Anemia. Neurologic Aspects of Sprue, Nontropical Sprue and Idiopathic Steatorrhea. Arch. Int. Med. 60: 272, 1937.
30. NIEWEG, H. O., VAN BUCHEM, F. S. P., AND KROESE, W. F. S.: Vitamin B_{12} and Pteroylglutamic Acid in the Treatment of Megaloblastic Anemias. Acta Med. Scand. 142: 45, 1952.
31. MOLLIN, D. L., AND ROSS, G. I. M.: Vitamin B_{12} Deficiency in the Megaloblastic Anaemias. Proc. Roy. Soc. Med. 47: 428, 1954.
32. GLASS, G. B. J., BOYD, L. J., GELLIN, G. A., AND STEPHANSON, L.: Uptake of Radioactive Vitamin B_{12} by the Liver in Humans: Tests for Measurement of Intestinal Absorption of Vitamin B_{12} and Intrinsic Factor Activity. Arch. Biochem. Biophys. 51: 251, 1954.
33. EVANS, J. R.: The Absorption of Vitamin B_{12} in the Megaloblastic Anaemias. Proc. Nutr. Soc. Lond. 15: 126, 1956.
34. NEALE, A. V., SMALLWOOD, W. C., AND SHIPPAM, F.: Prognosis of Celiac Disease, with a Comment on the Hematologic Characteristics. Am. J. Dis. Child. 50: 1502, 1935.
35. HARDWICK, C.: Prognosis in Coeliac Disease. A Review of Seventy-Three Cases. Arch. Dis. Child. 14: 279–294, 1939.
36. KRJUKOFF, A.: Anämie bei Sprue. Folia Haematol. 35: 329, 1928.
37. RHOADS, C. P., AND CASTLE, W. B.: The Pathology of the Bone Marrow in Sprue Anemia. Am. J. Pathol. 9: 813, 1933.
38. FRIEDLANDER, P. H., AND GORVY, V. Steatorrhoea.: A Review of 40 Patients with Particular Reference to Diagnosis. Brit. Med. J. 1: 809, 1955.
39. GARDNER, F. H.: Observations on the Cytology of Gastric Epithelium in Tropical Sprue. J. Lab. Clin. Med. 47: 529, 1956.
40. WANG, C. I., AND BOSSAK, E. T.: Hemorrhagic Manifestations in Idiopathic Sprue. This volume, page 143.
41. MOORE, M. J., STRICKLAND, W. H., AND PRICHARD, R. W.: Sprue with Bleeding from Hypoprothrombinemia. Arch. Int. Med. 97: 814, 1956.
42. RODRIGUEZ-MOLINA, R.: Fundamental Concepts in the Diagnosis of Sprue. Ann. Int. Med. 40: 33, 1954.
43. COHEN, B. S., MEYER, L. M., AND FADEM, R.: Sprue Refractory to Vitamin B_{12}; Satisfactory Response to Folic Acid. Ann. Int. Med. 36: 1533, 1952.

44. Israels, M. C. G., and Sharp, J.: Idiopathic Steatorrhoea (Non-Tropical Sprue) with Megaloblastic Anemia. Lancet 1: 752, 1950.

45. Tuck, I. M., and Whittaker, N.: Vitamin B_{12} in Idiopathic Steatorrhoea. Lancet 1: 757, 1950.

46. Miller, D. K., and Rhoads, C. P.: The Experimental Production of Loss of Hematopoietic Elements of the Gastric Secretion and of the Liver in Swine with Achlorhydria and Anemia. J. Clin. Investigation 14: 153, 1935.

47. Halsted, J. A., Swendseid, M. E., Gasster, M., and Lewis, P. M.: Absorption of Radioactive Vitamin B_{12} in Patients with Disease of the Small Intestine: Relation to Macrocytic Anemia. Tr. Am. Clin. Climat. Ass. 66: 18, 1954.

48. Reisner, E. H., Jr., Gilbert, J. P., Rosenblum, C., and Morgan, M. C.: Applications of the Urinary Tracer Test (of Schilling) as an Index of Vitamin B_{12} Absorption. Am. J. Clin. Nutr. 4: 134, 1956.

49. Callender, S. T., and Evans, J. R.: Observations on the Relationship of Intrinsic Factor to the Absorption of Labelled Vitamin B_{12} from the Intestine. Clin. Sc. 14: 387, 1955.

50. Mollin, D. L., and Ross, G. I. M.: Serum Vitamin B_{12} Concentrations of Patients with Megaloblastic Anaemia after Treatment with Vitamin B_{12}, Folic Acid, or Folinic Acid. Brit. Med. J. 2: 640, 1953.

51. Girdwood, R. H.: A Folic Acid Excretion Test in the Investigation of Intestinal Absorption. Lancet 1: 53, 1953.

52. Lopez, G. G., Milanes, F., Spies, T. D., Toca, R. L., Aramburu, T., and Lopez, H.: The Association of Hypoproteinemia with Severe Tropical Sprue. Am. J. Med. Sc. 218: 660, 1949.

53. Owren, P. A.: A Protein Synthesis Factor (P. S. Factor) Lacking in Pernicious Anemia and Related Macrocytic Anemias. Scand. J. Clin. Lab. Invest. 2: 241, 1950.

54. Mueller, J. F., Hawkins, V. R., and Vilter, R. W.: Liver Extract Refractory Megaloblastic Anemia. Blood 4: 1117, 1949.

55. Jones, E., Darby, W. J., and Totter, J. R.: Pernicious Anemia and Related Anemias Treated with Vitamin B_{12}. Blood 4: 827, 1949.

56. Darby, W. J., Kaser, M. M., and Jones, E.: The Influence of Pteroylglutamin Acid (A Member of the Vitamin M Group) on the Absorption of Vitamin A and Carotene by Patients with Sprue. J. Nutrition 33: 243, 1947.

57. Halsted, J. A., Swendseid, M. E., Lewis, P. M., and Gasster, M.: Mechanisms Involved in the Development of Vitamin B_{12} Deficiency. Gastroenterology 30: 21, 1956.

HEMORRHAGIC MANIFESTATIONS IN IDIOPATHIC SPRUE:
A Report of 25 Cases and Review of the Literature

CHUN I. WANG, M.D.
AND
ELAINE T. BOSSAK, M.D.
New York, New York

Severe bleeding is reportedly a rare manifestation of sprue (1, 2). When present it is a result in almost all instances of severe hypoprothrombinemia due to vitamin K deficiency (3–11). The most common sites of bleeding are the skin and subcutaneous tissues, although epistaxis, melena, hematuria, hemoptysis, menorrhagia and hemarthrosis have been reported. To our knowledge, no such complications have been observed in tropical sprue except where aplastic anemia with thrombocytopenia supervenes (12–14).

The present study reports 25 patients in whom hemorrhagic phenomena were a prominent feature of idiopathic sprue. Seven of these patients are presented in detail. These patients were encountered in a review of 82 sprue patients selected for this study from a larger number of patients observed at The Mount Sinai Hospital, New York City, from 1931 to 1956. A detailed analysis of the clinical observations of this group is presented elsewhere in the symposium (27).

CLINICAL MATERIAL

The total group included 27 men and 55 women ranging in age from 16 to 73 years at the time of first hospital admission with a mean age of 48 for the males and 45 for the females. The majority of patients had diarrhea with steatorrhea, abdominal distention and marked weight loss. All had evidence of malabsorption of carbohydrate and/or fat. In most instances an abnormal small bowel x-ray pattern was demonstrated, with dilatation, late segmentation and increased secretion. Symptoms had been present for from one month to 52 years before initial hospitalization; the average duration of symptoms was 6.2 years. Ten patients were observed only for the duration of hospitalization. Seventy-two patients were followed for a period of from six months to 22 years, with an average follow-up period of 5.1 years. Thirty of these patients are still under continuous observation at the present time. Thirteen patients died from the disease.

Twenty-two patients, eight men and 14 women, were from Puerto Rico. Because of the difficulty in setting the time of onset of the disease, the number of patients in this group who developed symptoms while in Puerto Rico could not be ascertained with certainty. Thus, the actual number who might be considered as true instances of tropical sprue could not be determined. Megaloblastic anemia was the presenting feature of these patients.

The group with hemorrhagic manifestations included seven men (mean age 48) and 18 women (mean age 43), two of whom were Puerto Rican. Symptoms

From the Department of Medicine, The Mount Sinai Hospital, New York, N. Y.

TABLE I

Clinical data of sprue patients with hemorrhagic manifestations

Case No.	Sex Age	Yr. of Admission	Bleeding Manifestations	Prothrombin Time (seconds) Patient/Control	Duration of Disease	Other Complications	Follow-up
1	F 52	1930	G. I. Bleeding	—	1 yr.	Tetany	Died 1933, no autopsy.
2	F 21	1932	Hemorrhage, post-tonsillectomy	—	5 mos.	Tetany, edema	Died 1944 in tetany. Autopsy — thrombosis dural sinus, cervical veins; fatty liver.
3	F 52	1933	Severe epistaxis	—	3 wks.	Megaloblastic anemia	—
4	F 60	1934	Melena, 4 yrs. before			Bone pain, Glossitis	Remission, 1948.
		1940	Occ. epistaxis	—	20 yrs.		
5*	F 50	1935	Ecchymoses, epistaxis	—	2 mos.	Osteoporosis, anemia	21 yrs., steroid therapy 6 yrs.
		1945	Hematuria, mod. ecchymoses	35/15			
		1950	Mod. ecchymoses	18/13		Tetany	
		"	Massive ecchymoses	100		Edema	
		1951	Hematuria	120			
		1952	Mod. ecchymoses	60/12			
6*	F 41	1935	Epistaxis, petechiae, ecchymoses, hematemesis, bleeding gums	—	3 yrs.	Tetany	Died, autopsy—multiple visceral hemorrhages.
7	M 64	1936	Epistaxis	—	—	—	Remission after 10 yrs., carcinoma of esophagus 16 yrs. later.
8	F 29	1937	Menorrhagia, 7 yrs.	—	3 mos.	Glossitis, megaloblastic anemia.	Remission, 1940
9	F	1940	Ecchymoses	—	10 yrs.	—	16 yrs., steroid therapy 6 yrs.
	30	1952	Ecchymoses	35/14		Volvulus of cecum (16)	
10*	F 60	1941	Epistaxis, bleeding gums, ecchymoses	55/24	1 yr.	Anemia, osteoporosis	Remission, 1943. Died, 1951 in an old age home.

TABLE I—*Continued*

Clinical data of sprue patients with hemorrhagic manifestations

Case No.	Sex Age	Yr. of Admission	Bleeding Manifestations	Prothrombin Time (seconds) Patient/Control	Duration of Disease	Other Complications	Follow-up
11*	M 73	1941 1944 1944	Ecchymoses, melena, petechiae Melena, epistaxis Hematuria and subconjunctival hemorrhage	70/23 120/30 (25%)	2 yrs.	Osteoporosis, anemia, hiatus hernia	—
12	M 16	1943	Hematemesis, melena	3%	3 mos.	—	Died 1944, autopsy—acute yellow atrophy of liver.
13	F 47	1945	G.I. bleeding, epistaxis, bleeding gums	47/15	1 yr.	Tetany	—
14	F 28	1945	Petechiae, purpura	32/18	2½ yrs.	—	—
15	F 29	1946	Purpura	31/24	3 yrs.	—	—
16*	M 50	1948	Ecchymoses	128/12	17 yrs.	Osteoporosis, fracture of femoral neck	8 yrs., steroid therapy 6 yrs.
17*	F 63	1949 1950	Ecchymoses	21/12 30/13	11 mos.	Osteoporosis,edema. Hemoglobinuria, E. Coli septicemia	Died 1951, no autopsy.
		1951	Melena	>3 min.		Tetany	
18	M 35	1951 1952	Melena Melena	14/12.5 —	1 yr.	—	Died 1953, autopsy—multiple ulcerations small intestine (15)
19	F 59	1953	Purpura	16.5/12.5	9 mos.	—	3 yrs. steroid therapy.
20	F 34	1953	Ecchymoses, epistaxis	—	2 yrs.	—	—
21	M 57	1953	Bleeding gums, purpura (1952)	—	2 yrs.	C.V.A. 1952	Steroid therapy, 2 yrs.
22	F 37	1954	Purpura (history)	—	5 yrs.	Tetany	2 yrs.
23*	M 36	1954	Ecchymoses, epistaxis	80 sec.	Several mos.	Old duodenal ulcer Edema, A. aerogenes septicemia	2 yrs., steroid therapy, 1 yr.
24	F 47	1954	Ecchymoses (history)	-	11 yrs.	Tetany	2 yrs., steroid therapy, 2 yrs.
25	F 41	1954	Gum bleeding	27/11	23 yrs.	Tetany, diabetes 30 yrs., edema	Steroid therapy, 2 yrs.,

* Indicates cases presented in detail.

had been noted in this group of patients for from one month to 23 years before admission, with an average duration of 3.6 years. Six of the deaths attributable to sprue occurred in this group of patients.

The clinical characteristics of the 25 patients with bleeding manifestations are presented in Table I. Severe bleeding into the skin (petechiae, ecchymoses, purpura) was the most frequently observed hemorrhagic manifestation, occurring on 19 occasions in 15 patients. Epistaxis was the next most common kind of bleeding and was observed in ten patients. Melena was noted by eight patients, bleeding gums by five, hematuria and hematemesis by two and post-operative hemorrhage and menorrhagia, each in one patient.

In 14 patients determination of the prothrombin time (one-stage) was performed at the time of bleeding. The values were abnormal in 13 instances, ranging from 21 seconds to more than three minutes (control 12 seconds). None of these patients had any evidence of liver disease. In all instances, after the administration of vitamin K the prothrombin time returned to normal. In patient 13, whose case is presented in detail elsewhere, melena was observed on two occasions and the prothrombin time was not prolonged. This patient subsequently died elsewhere and at autopsy multiple ulcerations of the small intestine were demonstrated (15).

Other complications noted in this group of patients were: tetany in nine instances and osteoporosis in six; edema was present in five patients; severe anemia was present in four; severe glossitis in two; septicemia in two; and volvulus of the cecum, an associated duodenal ulcer, unexplained hemoglobinuria and diabetes mellitus were each noted in one patient.

CASE REPORTS

Condensed case histories are presented for seven of these patients, three men and four women, in whom hemorrhagic phenomena were severe and fulminating.

Case 23

S. B., a 36-year old man, was hospitalized in April 1954 because of leg pains for five days and epistaxis for one day. He had noted intermittent fever for nine months; weakness, anorexia and a 14-pound weight loss in the preceding two weeks; and one to two watery bowel movements daily for several months. A duodenal ulcer diagnosed in 1940 recurred in 1945 and 1946. X-ray examinations performed in 1951 and 1952 revealed an old duodenal ulcer, retention of barium in the duodenum, coarsening of the mucosal pattern of the small bowel with dilatation and segmentation. On physical examination at admission in April 1954 he was emaciated and acutely and chronically ill. The temperature was 104°F., pulse 100 per minute and blood pressure 130/70. The lips and nostrils were excoriated and crusted with blood. The calves and extensor surfaces of both thighs were tender and warm. Large ecchymoses were noted over the left upper pretibial area. Laboratory studies are presented in Table II. The suspected diagnosis of leukemia was ruled out by negative peripheral blood and bone marrow examinations. The studies performed to determine the coagulation defect indicated severe hypoprothrombinemia. The platelet count was normal, 200,000 per cmm. with a normal bleeding time of five minutes. The fibrinogen content was also normal, 250 mg. per cent. The clotting time was prolonged to 25 minutes. The prothrombin time was markedly prolonged to 80 seconds. The prolonged prothrombin time of more than two minutes, obtained with a 10 per cent dilution, ruled out a labile factor deficiency. The

TABLE II

Laboratory Data of 7 Patients during Acute Episodes of Hemorrhagic Manifestations Due to Hypoprothrombinemia

Pt.	Date	HGB. gm.%	WBC cu. mm.	Plts. cu. mm.	Alb.	Glob.	Ca	Cholest.	Alk. P'tase. K.A.	Glucose Tol. Test		Vit. A Tol. Test		Caro-tene	Fecal Fat % Dry Wt.	
					gm.%		mg.%			mg.% 0	Max.	gamma % 0	Max.	gamma %	Neutral fat	Fatty acids
23. (S. B.)	Apr. '54	9.3	6,800	220,000	2.3	3.5	8.8	127	48	102	127	25	46	11	32	12
17. (R. B.)	May '49	9.1	8,000	120,000	3.8	2.8	9.6		24	60	103	29	82	38		
	Dec. '51	2.7	13,000	120,000	2.2	1.9	5.4	142	12						41†	
16. (P. S.)	July '48	9.9	5,250	190,000	3.9	1.4	9.1	200	28	80	110	32	37	9	20	28
11. (M. S.)	Mar. '41	50.0*	2,400				8.3								48†	
	Sept. '44															
10. (N. M.)	Mar. '41	46.0*	7,100	260,000	3.7	2.0	8.7	220	36	47	120	15		6	15.5†	
6. (I. H.)	July '35	14.0*	1,950	180,000			7.6			75	85					
5. (S. H.)	Aug. '45	8.6	5,600	185,000	2.8	1.6	8.6		15	80	130	53	78	16		
	July '50	8.8	6,000	140,000	3.0	2.7	6.9	143	31			15	87	38	50†	
	Sept. '50	4.5	6,700	120,000	2.0	1.6	7.3	143	18	91	100	20	29	5	17	40
	Apr. '52	10.2	6,500	190,000	3.6	2.6	8.7	160	8			56	83	21	23	39

* Expressed in per cent † Indicates total fecal fat, % dry wt.

absence of a circulating anticoagulant was proven by plasma-mixing experiments showing that addition of the patient's plasma to normal plasma did not prolong the clotting time of the latter. The blood culture was positive for *Aerobactor aerogenes*. Gastrointestinal x-ray examination confirmed the previous findings.

After vitamin K therapy the muscle pain and bleeding subsided. The clotting time returned to a normal of 11 minutes while the prothrombin time fell to a normal of 12.8 seconds. The presence of malabsorption, steatorrhea and small bowel deficiency pattern on x-ray suggested the diagnosis of non-tropical sprue as the etiology of the hypoprothrombinemia. The fever was attributed to septicemia and responded to Chloromycetin. The anemia was corrected by transfusion. The patient gained 12 pounds and was discharged.

The patient was readmitted in August 1954 for diarrhea, nausea and a weight loss of 17 pounds. The fingers were clubbed and the abdomen distended with visible loops of bowel. The prothrombin time was normal, 13.5 seconds (control 12 seconds). Therapy consisted of a high caloric-low fat diet, crude liver extract, parenteral vitamin B_{12}, oral iron, vitamins (including folic acid), deodorized tincture of opium, Banthine and calcium.

He was again hospitalized in October 1954 for bronchopneumonia associated with a relapse of the sprue syndrome. In August 1955, after development of pedal edema and a weight loss of 30 pounds, prednisone was started and the patient improved. He was maintained on 12.5 mg. of prednisone daily in addition to previous therapy. His weight rose to 150 pounds and all symptoms of sprue were controlled.

Comment. A 36-year old man, presenting with fever, skin and muscle hemorrhages, and epistaxis, was initially suspected of leukemia. Bleeding was due to severe hypoprothrombinemia, corrected by administration of vitamin K. There was associated septicemia. While in the Hospital, steatorrhea was present without diarrhea. Malabsorption and small bowel "deficiency pattern" were demonstrated, leading to a diagnosis of idiopathic sprue. Recurrent episodes of diarrhea and malnutrition supervened but were controlled by steroid therapy.

Case 17

R. B., a 63-year old woman, was hospitalized in May 1949 because of an ecchymosis covering the left upper extremity of four days duration, and weakness for three months. Nine months before she had been hospitalized because of leg pains, anorexia, fatigue and a 10-pound weight loss. Bone x-rays showed severe osteoporosis. The iliac marrow showed cells suggestive of myeloma. The patient was treated with stilbamidine and urethane. Physical examination at the present admission revealed a large ecchymosis of the left arm and forearm with swelling and warmth over the lower biceps. Clubbing of the fingers was present. Laboratory data revealed moderate anemia and malabsorption with steatorrhea (Table II). The bone marrow showed increased erythropoiesis and numerous megakaryocytes. Prothrombin time was 21 seconds (control 12 seconds). A barium meal revealed an abnormal small bowel pattern with dilatation, segmentation and thickened folds. The bleeding was ascribed to hypoprothrombinemia resulting from malabsorption. After administration of vitamin K the prothrombin time was normal, 12 seconds. The patient was treated with diet, vitamins, including B_{12} and D, and calcium. At no time during this admission was there any diarrhea.

The patient was subsequently hospitalized three times for severe episodes of diarrhea between August 1949 and June 1950, and once in March 1950 for unexplained hemoglobinuria. The serum calcium fell to 7.4 mg. per cent and the prothrombin time was prolonged, 30 seconds (control 13 seconds). She became cachectic with ankle edema, dry skin, thin hair and marked atrophy of the tongue margins. The patient was apparently refractory to the conventional therapy but refused adrenocorticotrophic hormone. She had an episode of shaking chills and fever with a positive blood culture for *E. coli*. Transfusions were given frequently. On occasion, melena was noted. She was hospitalized for the last time in December 1951 because of increased weakness, bone pain, edema and melena. There was pallor, abdominal distention and tenderness, and carpopedal spasm. She had severe anemia, hypocalcemia and hypoalbuminemia (Table II). The prothrombin time was more than three minutes (Table I). She became semicomatose and disoriented, despite supportive measures. Following administration of intravenous ACTH she improved temporarily but three weeks later developed severe tetany, lapsed into coma and died. Post-mortem examination was refused.

Comment: A 63-year old woman was hospitalized because of massive ecchymoses and bone pain attributed to severe osteoporosis. Bleeding was ascribed to hypoprothrombinemia corrected by administration of vitamin K. Steatorrhea was found without diarrhea. X-ray of the small bowel showed a deficiency pattern. Subsequently, the patient had severe diarrhea, anemia, edema, tetany and again hypoprothrombinemia with melena. She had one episode of unexplained hemoglobinuria and a transient septicemia. She deteriorated progressively and died two and one-half years after the initial bleeding episode.

Case 16

P. S., a 50-year old man, was hospitalized in July 1948 because of multiple painful ecchymoses of the buttocks and extremities following venipuncture and intramuscular injections. In 1931 the patient first noticed diarrhea with two to four watery, foul, fatty, tan-colored bowel movements daily. There was flatus and abdominal distention. In 1944, he was put on a bland diet with bananas supplemented with vitamins, liver extract and folic acid. Diarrhea persisted and he lost 44 pounds. On physical examination, the patient was pot-bellied and poorly nourished. The blood pressure was 100/60. Large painful ecchymoses were noted over the right arm and the buttocks extending down to the right ankle. The fingers and toes were clubbed. Deep tendon reflexes were absent. Vibration sense was absent below the waist. Other laboratory findings pointed to a malabsorption syndrome (Table II). Bone survey revealed generalized osteoporosis. X-ray examination of the small bowel revealed a deficiency pattern from the duodenum through the terminal ileum. Pancreatic function was normal. Cerebrospinal fluid was normal. Hematological work-up revealed a prolonged prothrombin time, 128 seconds (control 12 seconds), which promptly returned to normal, 15 seconds (control 15 seconds), following injection of vitamin K. The Rumpel-Leede test was negative. The ecchymoses disappeared and the patient was discharged with massive doses of vitamin B_{12}.

The patient was readmitted in May 1951 and in July 1952 for exacerbations of the sprue syndrome. Symptomatic control was achieved with steroid therapy on both occasions.

In December 1954 he sustained a partial fracture of the left femoral neck which was treated by pinning. His neurological findings remained stationary. He is maintained on 10 milligrams of prednisone a day at the present time and weighed 127 pounds.

Comment: A middle-aged man was admitted for painful massive ecchymoses of the buttock and extremities following venipuncture and intramuscular injections. He had a history of steatorrhea and weight loss for 17 years. The diagnosis of non-tropical sprue complicated by hypoprothrombinemia was made. He had moderate osteoporosis with fracture of the left femur, and neurological findings simulating peripheral neuropathy and a typical, subacute combined degeneration. He had been symptomatically controlled on steroid therapy for five years

Case 11

M. S.*, a 73-year old man, was hospitalized in March 1941 because of melena for several days and ecchymoses over both hands. He had diarrhea with steatorrhea for two years and a history of ecchymoses. On examination he appeared emaciated and chronically ill with lemon-yellow pallor. The blood pressure was 90/60. The tongue was smooth and beefy-red. Petechiae were present on the hard palate and ecchymoses on the dorsum of both hands. There was moderate abdominal distention. Laboratory studies are presented in Table II. The prothrombin time on admission was 70 seconds (control 23 seconds). Following vitamin K therapy the prothrombin time was 23 seconds. X-rays of the gastrointestinal tract revealed a small hiatus hernia, in addition to a deficiency pattern. Osteoporosis was noted. He was treated with blood transfusions and vitamins with improvement.

He was hospitalized again in August 1944 because of severe melena and epistaxis. The prothrombin time was 120 seconds (control 30 seconds). In September 1944 hematuria and a subconjunctival hemorrhage were observed with a prothrombin time of 25 per cent. Bleeding stopped after administration of Hykinone and ascorbic acid. He was placed on a regimen of liver injections, parenteral calcium and oral vitamin B complex, vitamin C and K. He was last observed in November 1944.

Comment: An elderly man developed diarrhea and steatorrhea two years before hospitalization for melena and ecchymoses. The prolonged prothrombin time became normal after vitamin K therapy. Three years later he had severe melena, epistaxis and hematuria associated with marked hypoprothrombinemia.

Case 10

N. M., a 60-year old woman, was hospitalized in March 1941 because of swollen ankles, bleeding gums and epistaxis of three days' duration and ecchymoses on the extremities for one day. One year before she had been told she had seven gm. per cent hemoglobin and was treated with iron and vitamins. Physical examination revealed a thin, pale woman with large ecchymoses on the right arm, from the axilla to the antecubital fossa, and on the inner aspect of the right thigh. Slight pitting pretibial edema was present. Laboratory examinations are noted in Table II. The bone marrow was megaloblastic. Dark adaptation was subnormal. Bleeding time was three minutes and coagulation time 11 minutes. Fibrinogen was normal and the Rumpel-Leede test negative. Prothrombin time was prolonged to 47 and 55 seconds (control 24 and 26 seconds, respectively). X-ray of the small bowel revealed a typical deficiency pattern. The bones showed osteoporosis. A diagnosis of non-tropical sprue without diarrhea with complicating hypoprothrombinemia was made. She was given a high protein diet, intramuscular liver extract and oral vitamin K. The prothrombin time returned to normal after addition of bile salts. She was given vitamins A and D, calcium and iron and improved. She was followed in the clinic for three years in good condition, except for a transient episode of peripheral neuritis which responded to thiamine. She received liver extract sporadically. She remained in remission until her death in a home for the aged in 1951.

Comment: A 60-year old woman with a history of anemia and weight loss presented with epistaxis, bleeding gums and extensive ecchymoses of her extremities. She had a severe megaloblastic anemia. Despite absence of diarrhea, clinical and laboratory findings established the diagnosis of non-tropical sprue complii cated by hypoprothrombinemia. The latter was corrected by vitamin K and bile salts. The patient remained in remission until her death ten years later.

---

* We should like to thank Dr. Burrill Crohn for permission to include this patient.

Case 6

I. H., a 41-year old woman, was hospitalized in July 1935 because of tibial pain for one week and edema for five weeks. She had lifelong diarrhea with five to six bowel movements daily and weakness and dyspnea for three years. She was dwarfed and extremely pale. Her temperature was 102°F., pulse 120 per minute and blood pressure 95/60. Petechiae were noted over the lower extremities. There were fundal hemorrhages. The tongue was smooth and atrophic. The liver was palpable two fingers-breadth below the costal margin. The forearms were bowed. There was generalized bone tenderness. Laboratory data revealed severe anemia and hypocalcemia in association with malabsorption (Table II). Bone x-rays showed old rickets. Small bowel x-rays showed moderate distention. She was treated with liver extract, transfusions and iron. She was readmitted twice within three months for diarrhea, vomiting and weight loss associated with recurrent nosebleeds, hematemesis, bleeding gums and painful swelling of the left thigh. There was bilateral carpopedal spasm and a hematoma covering the left buttock, thigh and leg. The bleeding time was five and one-half minutes, clotting time 29 minutes, and fibrinogen level normal. She showed no response to multiple transfusions and calcium and died 12 days after the last admission. Post-mortem examination revealed multiple hemorrhages into the pleura, peritoneum, skin, mucous membranes, anterior mediastinum and renal pelvis. The intestine showed congestion of the mucosa and non-iron pigment granules in the muscularis. The liver and kidneys were fatty. The pathological findings have been presented in detail previously (17).

Comment: A 41-year old woman with a lifelong history of diarrhea was hospitalized with severe anemia and hypocalcemia and evidence of malabsorption. Petechiae were noted. She developed recurrent nosebleeds, severe hematemesis, bleeding gums and a large hematoma. There was low-grade tetany. The clotting time was prolonged. Despite multiple transfusions and massive calcium therapy bleeding persisted and the patient died.

Case 5

S. H., a 50-year old woman, was seen at the Consultation Service of this hospital in 1935 because of weakness, epistaxis and easy bruising for two months. She had four to five foul, bulky bowel movements daily, abdominal cramps and a ten pound weight loss. Physical examination revealed a thin, pale woman with marked dorsal kyphoscoliosis and protuberant abdomen. She persistently showed petechiae and ecchymoses on the extremities. She was moderately anemic and hypocalcemic. She had generalized osteoporosis. Steatorrhea, malabsorption and abnormal small bowel x-ray pattern led to the diagnosis of nontropical sprue. The symptoms were controlled for ten years on bland diet, liver extract and calcium injections. Epistaxis and ecchymoses continued.

In August 1945 the patient noticed frank hematuria for one day and a large ecchymosis over the right knee. The stool showed a four plus guaiac reaction. Intravenous pyelogram, cystoscopic examinations and barium meal study for site of bleeding were negative. The prothrombin time was 35 seconds (control 15 seconds), and coagulation time 27 minutes. Bleeding stopped after a blood transfusion and Hykinone administration.

The patient was hospitalized in July and September 1950 with two episodes of extensive ecchymosis. Microscopic hematuria and guaiac positive stools were present. The patient had large confluent ecchymoses on all extremities and many petechial spots on the buccal mucosa. Her blood pressure was 70/40. A grade III systolic murmur was heard over the precordium. Laboratory data showed severe anemia, hypoalbuminemia and hypocalcemia (Table II). The bleeding time was six minutes and coagulation time 36 minutes, clot retraction adequate. Prothrombin time was markedly prolonged to 100 seconds (control 13 seconds). Prothrombin consumption was normal. Massive blood transfusions and large doses of vitamin K were given. Hemorrhagic manifestations subsided completely.

In December 1950, two months after cortisone therapy was instituted, she was admitted in extreme carpopedal spasm, with a serum calcium of 5.8 mg per cent.

In April 1951, an exacerbation of the sprue syndrome was precipitated by cortisone withdrawal. Microscopic hematuria, guaiac positive stools and intermittent crops of skin petechiae were observed and the prothrombin time was prolonged to over two minutes. Steroid therapy was reinstituted.

She was hospitalized for tetany following Mercuhydrin in August 1951. Skin petechiae persisted and an episode of ecchymoses involving both hands, forearms, tongue and buccal mucosa occurred in April 1952 following an exacerbation of diarrhea. Hypoprothrombinemia was again present (Table I). Steroid therapy was increased and oral vitamin K and C were added with control of symptoms.

From 1953 through 1956 the patient was maintained asymptomatic on steroid therapy with supplemental multiple vitamins and calcium.

Comment: A 50-year old woman had various hemorrhagic manifestations during 21 years of observation. Frank hematuria, epistaxis, multiple ecchymoses, petechiae, and hemorrhage into the tongue and buccal mucosa occurred repeatedly. Hypoprothrombinemia was constant. There was secondary anemia, extensive osteoporosis and hypocalcemia with tetany. After steroid therapy, only one major bleeding manifestation occurred. She has been maintained in clinical remission on a minimal dose of steroid for six years.

DISCUSSION

In 1927, Fanconi described three patients with celiac disease and a hemophilia-like hemorrhagic diathesis different from scurvy in which the clotting time was prolonged and the platelets normal (18). He later described this syndrome as resembling fatal fulminating purpura (19, 20). In 1938, he suggested that the bleeding might be caused by a deficiency of vitamin K and thereby of prothrombin (21).

Subsequently, hypoprothrombinemia was demonstrated in patients with non-tropical sprue (Table III) (3, 4). In 1940, Kark, Souter and Hayward (5) reported a patient with sprue who developed a severe hemorrhagic tendency with marked hypoprothrombinemia corrected by administration of oral synthetic vitamin K. Since then six reports of similar instances of sprue complicated by hemorrhages have appeared in the literature (6–11). Details of these patients are presented in Table III. The findings in this group of patients are similar to those in the present series as regards duration of disease, bleeding manifestations, marked hypoprothrombinemia, correction by administration of vitamin K, and association with other complications, particularly tetany.

Reviews of large series of patients with idiopathic sprue reveal the absence of bleeding and hypoprothrombinemia in patients with the tropical variety (12–14) while the incidence in non-tropical sprue is of the order of 10 to 22 per cent (2, 17). In the present series bleeding was noted in 30.5 per cent of the total group. Only two of the patients from Puerto Rico had any hemorrhagic manifestations. If these patients are excluded, the incidence of bleeding rises to 40 per cent of patients with non-tropical sprue. Massive bleeding as a prominent presenting feature occurred in 11.7 per cent of this group of patients.

The seven patients presented in detail in this study showed hemorrhagic mani-

TABLE III

Previously Reported Cases of Sprue Complicated by Bleeding

Author	Year	Age	Sex	Hemorrhagic Manifestations	Prothrombin Time (sec.)	Clotting Time	Symptoms	Therapy
Bassett et al (3)	1939	36	M	Hemarthrosis, ecchymoses, hematuria, melena	—	40′	Diarrhea, 4 yrs., tetany	Transfusions
Kantor (4)	1940	45	F	Melena	—	(prolonged)	Diarrhea, tetany	Died
Kark, Souter & Hayward (5)	1940	62	M	Purpura, hematuria, melena	96/25	20′	Diarrhea, 3 yrs., tetany	Vit. K (oral, synthetic)
Allen (6)	1941	—	F	Menorrhagia, ecchymoses, bleeding gums	(15%)		Diarrhea, 3 yrs., tetany	Alfalfa conc., synthetic vit. K & K_1
Alper (7)	1942	57	F	Hemarthroses, purpura, ecchymoses	26/15		Pathological fractures, 7 yrs., osteoporosis, no diarrhea, steatorrhea with 39% fecal fat	—
Collins & Hoffmanns (8)	1943	—	—	Hemoptysis, hematuria	41		Diarrhea, 4 mos., calcium 8.3	I.V. vit. K, previous sulfa therapy
Ingelfinger (9)	1943	31	F	Hematuria, epistaxis, purpura	<1%		Diarrhea, 2–3 mos., tetany	—
Butler & Young (10)	1955	39	F	Recurrent ecchymoses, menomentrorrhagia	>24	27′	Diarrhea, 2 wks., calcium 8.6, osteomalacia	Vit. K
Scharfman & Propp (11)	1956	53	F	Purpura, melena	>4 mins.	> 24 hrs.	Diarrhea, 4 yrs., calcium 8.0	Vit. K and blood transfusions

festations as a major complication of sprue. Three patients, cases 10, 17 and 23, did not have diarrhea during the acute episode of bleeding manifestations, but steatorrhea was present in all. Case 17 developed diarrhea after the diagnosis of sprue was established. On the other hand, case 6 had diarrhea for 41 years and case 16 had diarrhea for 17 years before developing hemorrhagic complications. Hypoprothrombinemia (vitamin K deficiency) was proven the cause of hemorrhagic manifestations in all instances except case 4 who was hospitalized prior to the discovery of vitamin K. Hypoprothrombinemia, therefore, seems to be related to malabsorption of fat rather than to diarrhea. The possibility that the sprue syndrome may be the cause of bleeding due to unexplained hypoprothrombinemia should be borne in mind even in the absence of the full-blown clinical picture of sprue.

Vitamin K is a fat-soluble vitamin which is present in certain vegetables and absorbed from the jejunum. It is also synthesized in the intestine by bacterial flora. Only small amounts are stored in the body. A very small amount is necessary to maintain plasma prothrombin above the critical level (a few micrograms) (22). Deficiency of vitamin K in sprue may be due to inadequate dietary intake (low fat diet), deficient synthesis due to alteration of intestinal flora, malabsorption from the intestine, or increased loss in the stools. Hemorrhages occur in patients whose diets have not been restricted in fat and who do not have diarrhea, suggesting that these factors are not responsible for vitamin K deficiency. The importance of alterations in intestinal flora in the etiology of the sprue syndrome has been emphasized by Frazer (23). None of the patients showed any impairment of liver function. None showed clinical jaundice. In one case that came to autopsy, case 4, the liver showed only minimal fatty changes. Prothrombin deficiency in these patients was not due to a defect in synthesis as seen in liver disease. It seems apparent, therefore, that malabsorption is the primary cause of deficiency in vitamin K.

Hypocalcemia was present in all of the seven patients. Four had manifest tetany. All except one had marked osteomalacia and one patient had sustained a pathological fracture of the femoral neck. These findings may be a reflection of deficiency of vitamin D as well as of calcium. Similar findings were noted in the patients with hemorrhagic phenomena reported by others (Table III). Of these nine patients, five had tetany, one had pathological fractures, one had osteomalacia and the remaining two had slight hypocalcemia.

Five patients had a hypochromic anemia and an erythroid bone marrow. One patient had a macrocytic anemia (case 16). Case 10 was the only patient to show a megaloblastic bone marrow. In contrast, 80 per cent of the sprue patients from Puerto Rico included in this review presented with macrocytic anemia or a megaloblastic bone marrow. Most of these patients responded favorably to liver extract intramuscularly. That megaloblastic anemia is not a necessary feature of the sprue syndrome in Puerto Rico has been demonstrated recently by Gardner (24). Therefore, in non-tropical sprue bleeding manifestations (hypoprothrombinemia) which are not too uncommon are usually associated with hypocalcemia, tetany and extensive osteoporosis. In the tropical variety, these complications are rare and megaloblastic anemia may be a more consistent feature of the disease, at least among the usual Puerto Rican patients.

It is of interest that two of the seven patients had septicemia due to gram-negative organisms usually found in the intestine. This complication has been rarely observed in sprue.

Institution of steroid therapy in three of the seven patients resulted in a marked decrease in the incidence of hemorrhagic manifestations (cases 5, 16, 23). This is especially evident in case five who had crops of skin petechiae intermittently during 21 years of observation. Massive hemorrhages occurred three times within two years prior to the institution of steroid therapy. Only one minor episode of ecchymoses was observed in the six years during which she was maintained on minimal doses of steroids. Both patients 16 and 23, who were also on steroid therapy, had no recurrence of bleeding after the initial episode. Steroid therapy apparently improved intestinal absorption (25, 26) and thereby sufficient vitamin K was available to maintain normal plasma prothrombin levels.

SUMMARY

Eighty-two sprue patients, 27 men and 55 women, observed at The Mount Sinai Hospital from 1931 to 1956 were reviewed for incidence of hemorrhagic manifestations. Twenty-five patients, seven men and 18 women, exhibited bleeding with severe hypoprothrombinemia directly attributable to malabsorption of vitamin K. Severe skin bleeding (petechiae, ecchymoses, purpura) was most frequently observed; although epistaxis, bleeding gums, melena, hematuria, hematemesis and menorrhagia were also encountered. Seven patients, three men and four women, in whom hemorrhagic phenomena were a prominent presenting feature requiring hospitalization are reported in detail. These cases illustrate that hemorrhagic manifestations of sprue can be fulminating although the primary disease is obscure. The importance of malabsorption of vitamin K as the cause of hypoprothrombinemia in sprue is stressed and the possible role of steroid therapy in correction of this malabsorption is discussed.

REFERENCES

1. Snell, A. M.: Tropical and Non-tropical Sprue. Ann. Int. Med., 12: 1632, 1939.
2. Cooke, W. T., Peeney, A. L. P., and Hawkins, C. F.: Symptoms, Signs and Diagnostic Features of Idiopathic Steatorrhea. Quart. J. Med., 22: 59 (No. 85), 1953.
3. Bassett, S. H., Keutmann, E. H., Hyde, H. V. Z., Van Alstine, H. E., and Russ, E.: Metabolism in Idiopathic Steatorrhea 1. The Influence of Dietary and Other Factors in Lipid and Mineral Balance. J. Clin. Invest., 18: 101, 1939.
4. Kantor, J. L.: Further Experience with the Roentgen Diagnosis of Idiopathic Steatorrhea. Arch. Int. Med., 65: 988, 1940.
5. Kark, R., Souter, A. W., and Hayward, J. C.: A Hemorrhagic Diathesis in Idiopathic Steatorrhea: Observations on its Association with Vitamin K Deficiency. Quart. J. Med., 9: 247, 1940.
6. Allen, J. G.: The Comparative Prothrombin Responses to Vitamin K and Several of its Substitutes in a Case of Non-tropical Sprue. New Eng. J. Med., 224: 195, 1941.
7. Alper, J. M.: The Hemorrhagic Tendency in Sprue. Rev. Gastroent., 9: 340, 1942.
8. Collins, E. N., and Hoffman, A. D.: Hemoptysis and Hematuria in Sprue. Cleveland Clinic Quart., 10: 105, 1943.

9. Ingelfinger, F. J.: The Diagnosis of Sprue in Non-tropical Areas. New Eng. J. Med., 228: 180, 1943.
10. Butler, J. J., and Young, L. E.: Idiopathic Steatorrhea with Hemorrhagic Manifestations due to Prothrombin Deficiency. N. Y. State J. Med., 55: 532, 1955.
11. Scharfman, W. B., and Propp, G.: Prolonged Diarrhea with Near-fatal Hemorrhage due to Hypoprothrombinemia. Ann. Int. Med., 44: 385, 1956.
12. Castle, W. B., Rhoads, C. P., Lawson, H. A., and Payne, G. C.: Etiology and Treatment of Sprue: Observations on Patients in Puerto Rico and Subsequent Experiments in Animals. Arch. Int. Med., 56: 627, 1935.
13. Stefanini, M.: Clinical Features and Pathogenesis of Tropical Sprue. Medicine, 27: 379, 1948.
14. Rodriguez-Molina, R.: Fundamental Concepts in the Diagnosis of Sprue. Ann. Int. Med., 40: 33, 1953.
15. Himes, H. W., Gabriel, J. B., and Adlersberg, D.: Previously Undescribed Clinical and Post-mortem Observations in Non-tropical Sprue: Possible Role of Prolonged Corticosteroid Therapy. Gastroenterology, 32: 60, 1957.
16. Glazer, I., and Adlersberg, D.: Volvulus of the Colon: A Complication of Sprue. Gastroenterology, 24: 2, 1953.
17. Adlersberg, D., and Schein, J.: Clinical and Pathological Studies in Sprue. J.A.M.A., 134: 1459, 1947.
18. Fanconi, G.: Beiträge zum Chemismus und zur Hämatologie des Herterscher Infantilismus. Monatschr. f. Kinderh., Leipz. 37: 454, 1927.
19. Fanconi, G.: Der intestinale Infantilismus und ähnliche Formen der chronischen Verdauungsstörung: ihre Behandlung mit Früchten und Gemüsen, Berlin, 1928.
20. Fanconi, G.: Der intestinale Infantilismus (Coeliakie) Klin. Wchnschr., Berlin, 9: 553, 1930.
21. Fanconi, G.: Zöliakie; Deutsch. med. Wchnschr. 64: 1565, 1938.
22. Warner, E. D.: In Clinical Nutrition, Chap. 17, Edited by N. Jolliffe, F. F. Tisdall and P. R. Cannon. P. B. Hoeber, Inc., 1950.
23. Frazer, A. C.: Fat Metabolism and the Sprue Syndrome. Brit. Med. J., 2: 769, 1949.
24. Gardner, F. H.: A Malabsorption Syndrome in Military Personnel in Puerto Rico. A.M.A. Arch. Int. Med., 98: 44, 1956.
25. Adlersberg, D., Colcher, H., and Drachman, S. R.: Studies on the Effects of Cortisone and Pituitary Adrenocorticotropic Hormone (ACTH) in the Sprue Syndrome. Gastroenterology, 19: 674, 1951.
26. Taylor, A. B., Wollaeger, E. E., Comfort, M. W., and Power, M. H.: Effect of Cortisone in Non-tropical Sprue (Idiopathic Steatorrhea). Gastroenterology 20: 203, 1952.
27. Bossak, E. T., Wang, C. I., and Adlersberg, D.: Clinical Aspects of Malabsorption Syndrome. This volume, page 112.

NEUROLOGIC MANIFESTATIONS IN THE MALABSORPTION SYNDROME

WALTER SENCER, M.D.

New York, N. Y.

In considering the neurologic manifestations of the malabsorption syndrome, we include celiac disease of children, tropical sprue and non-tropical sprue (idiopathic steatorrhea). In celiac disease of children, neurologic sequellae are not mentioned, except as rarities (1–3). With reference to tropical sprue, there is no note of neurological complications in Grodwohl's textbook on "Tropical Medicine" (4). In a paper on post-mortem findings on tropical sprue, Mackaie and Fairley (5) state that in their clinical experience there have been no signs or symptoms of central nervous system or peripheral nervous system involvement. In a hundred cases of sprue in Puerto Rico, 14 per cent were found to have numbness of the toes and fingers, formications and paresthesias, 10 per cent had decreased or absent deep tendon reflexes and decreased or absent vibration sense below the iliac crest (6). The conclusion was that in tropical sprue absence of neurological manifestations was the rule. Thaysen (7) described in his monograph on non-tropical sprue frequent occurrence of paresthesias of the hands and toes in the absence of anemia. He never was convinced of the presence of any actual disturbance of sensibilities despite some transient neurological findings such as Babinski signs and clonus. Thaysen believed that neurological abnormalities in non-tropical sprue were rare as well as inconspicuous.

This report is an analysis of the neurological manifestations in 94 cases of the malabsorption syndrome studied in the clinics and wards of The Mount Sinai Hospital for a period of years, including follow-up observations averaging seven years.

CLINICAL MATERIAL

Special studies were performed in patients 1, 2, 3, 4, 14, 15, 45 and 46, while the remainder were subjected to the routine neurological examination. Detailed case histories of the first four patients are presented.

CASE REPORTS

Case 1

A 43 year old white man was well until 1942 when he began having watery non-bloody diarrhea, vomiting, weakness and concomitant 16 pound weight loss; his bowel movements were foul smelling. He was hospitalized for six weeks with improvement. In 1945, he was admitted to another hospital for four months with recurrence of diarrhea and vomiting. In 1948, he was readmitted for similar symptoms and a spontaneous fracture of the left hip and, in 1949, for a relapse of diarrhea, extreme gaseous distension of the abdomen and pneumonia. Blood transfusions were administered at that time, as well as folic acid and vitamin B_{12} He stayed 14 months and was discharged on liver injections and vitamin B_{12}. The patient was unable to work after 1950, and remained in a nursing home part of 1952. From November

---

From the Department of Neurology, The Mount Sinai Hospital, New York, N. Y.

1952 to the time of this admission he was at a hospital where he received injections of ACTH. For about two years the patient had noticed stiffness and numbness of the extremities, inability to move his arms and legs and marked paresthesias. This progressed to a degree where he could barely walk and he could stand only when holding on to something. At this admission to The Mount Sinai Hospital (1953), diarrhea was intermittent, watery and foul-smelling. There was no vomiting and the appetite was good (his weight stabilized at 110 pounds, highest normal weight 145 pounds). The patient was raised in Italy, but has lived in New York City since age 19. There was no family history of diarrhea or pernicious anemia. He denied any parasitic infections. Past history revealed that he had had an operation for a cataract of the left eye 1948 (total amaurosis of left eye since 1942).

Physical examination in December 1953 revealed normal temperature, pulse, and respiration. The blood pressure was 90/50. The patient was an emaciated, chronically ill, white man with marked dorsal kyphoscoliosis, very short stature, who was unable to walk unassisted. The skin of the arms and face was bronze in color and there was brown spotty pigmentation of extremities. There was no vision in left eye and the left pupil did not react to light. There was brown spotty pigmentation of the lips and buccal mucosa. The tongue was pale, smooth, and presented cheilosis. The chest showed marked dorso-kyphoscoliosis and increased anterior-posterior diameter with flaring of ribs. The abdomen was distended but not tender. Bowel sounds were hypoactive.

Neurological examination: The cranial nerves were intact, except for the blind left eye and left internal strabismus. There was marked weakness of the lower extremities, mainly in the proximal musculature. The hand grip was weak. The Romberg test was positive. He was markedly ataxic with severe heel-to-knee dysfunction. The deep tendon reflexes were absent throughout. There were no pathological reflexes. Vibration sense was absent below the iliac crest; it was also absent distally below both elbows. Position sense was absent in all the toes and in the fingers of the left hand. There was impairment of position sense in the fingers of the right hand and marked astereognosis bilaterally. There was hyperpathia of the soles of the feet.

Laboratory analyses: Urine, negative, except for occasional trace of 1 plus albumin; hemoglobin, 4.75 gm. per cent; red blood cell count, 2.53 million per cu. mm.; hematocrit, 21; white blood cell count, 5700 per cu. mm.; platelets, 230,000 per cu. mm.; MCV, 83; MCH, 19; MCHC, 23; extreme hypochromia, marked anisocytosis, many macrocytes and microcytes; sedimentation rate, 30 mm. per hour (Westergren); BUN, 10 mg. per cent; CO_2, 52 vol. per cent; chloride, 105 mEq. per liter; sodium, 133 mEq. per liter; potassium, 4.8 mEq. per liter; serum protein, 6.8 gm. per cent; A/G ratio, 3.6/3.2; calcium, 5.9 mg. per cent; phosphorus, 3.5 mg. per cent; alkaline phosphatase, 24 King-Armstrong units; bilirubin, 0.2 mg. per cent; cholesterol, 93 mg. per cent, esters, 70 mg. per cent; prothrombin time, 16 seconds (control, 13 seconds); phospholipids, 93 mg. per cent; serum iron, 45 μg. per cent; total iron binding capacity, 361 μg. per cent; fasting carotene level, 8 μg. per cent. Vitamin A tolerance: fasting, 16 μg. per cent; four hours, 13; six hours, 19; eight hours, 18 μg. per cent. Oral glucose tolerance (100 gm. glucose): fasting blood sugar, 97 mg. per cent; half hour, 104; one hour, 100; two hours, 200; three hours, 90 mg. per cent. Intravenous glucose tolerance test: half hour, 160 mg. per cent; one hour, 140; one and one-half hours, 150; two hours, 88 mg. per cent. Marrow iron tolerance test: fasting sample, 48 μg. per cent; half hour, 43; one hour, 56; two hours, 100; three hours, 95; four hours, 150; five hours, 195; six hours, 176 μg. per cent (impaired absorption). Gastric analysis revealed free hydrochloric acid to be present. Spinal fluid was normal. Bone marrow: normal cellularity with slight increase in megakaryocytes, many white blood cells larger in size and with more band cells than usual; many pro-erythroblasts and erythroblasts, some with atypical nucleus structure resembling megaloblasts; many normoblasts were basophilic and polychromatophilic. X-ray examinations revealed a fairly marked degree of demineralization of all bones. The right hemithorax was narrower than left. There was an old fracture of right scapula, right clavicle and lateral third rib and neck of left femur. Focal areas of atelectasis above both diaphragms were seen. Small bowel studies revealed no definite evidence of mucosal abnormality, the bowel loops were somewhat dilated and some segmentation and irregularity of contour suggesting mucous secretion. There was tremendous dilatation of the large bowel, however the terminal ileum was normal.

The patient was started on parenteral vitamin B_{12}, 1000 micrograms daily, which he received throughout his hospital stay. A fall in hemoglobin to 3.9 gm. per cent necessitated blood transfuions. Bone marrow aspiration following an injection of 3000 micrograms of B_{12} showed a normoblastic erythropoiesis. After approximately three weeks on B_{12} alone, three milliliters of crude liver extract daily was added to the regimen and continued throughout hospitalization. Despite vitamin B_{12}, liver extract and transfusions, the patient's hemoglobin which had risen to 8.7 gm. per cent, fell to 5.8. Following radioactive iron studies, the patient was started on a course of intravenous iron totalling two grams over the course of 20 days. At its completion, the hemoglobin had risen to 11.9 gm. per cent with a concomitant feeling of well being. At this point, the following studies were repeated and showed no change from those on admission: glucose tolerance test, vitamin A tolerance test, small bowel x-rays; serum cholesterol rose to 122 mg. per cent, esters to 87 mg. per cent and phospholipids to 151 mg. per cent. There was no change in the neurologic status. The patient was then started on physiotherapy which continued throughout hospitalization. He had gained 14 pounds to this point, but the diarrhea persisted intermittently along with abdominal distension. After six weeks of physiotherapy, the patient was able to walk unaided with crutches and the range of motion had increased in the involved joints. The patient was started on hydrocortisone, 80 mg. daily. He felt stronger and his bowel movements decreased to one daily. Hydrocortisone was then reduced to 60 mg. daily. After six weeks on hydrocortisone a vitamin A tolerance test was still flat and it was noted that the patient's hemoglobin had fallen again to a level of 8.4 gm. per cent; therefore, a second course of intravenous iron was given, again totalling two grams, with a rise in hemoglobin to a level of 12 gm. per cent. Blood studies then revealed red blood cell count, 5.15 million per cu. mm.; hematocrit, 45.5; MCV, 88; MCH, 23; MCHC, 26. Re-evaluation of the neurological status prior to discharge showed no evidence of improvement or progression. Repeat small bowel x-ray at that time showed normal transit time and considerable change in the appearance of the small bowel as compared with previous films. Dilatation was less marked and the increase in secretion probably present was to a much lesser degree than previously noted. The evidence of late segmentation was also less pronounced. Serum cholesterol had risen to 215 mg. per cent.

The patient was then transferred to a chronic disease hospital where he was seen in the summer of 1956 and gave a history with respect to his neurological symptoms as follows: for six or seven years there had been numbness (pins and needles sensations) of the right hand which then spread to involve the left hand and eventually both lower extremities. He described the feelings also as stiffness and tightness. In 1952, he developed further numbness of the feet and began to have progressive difficulty in walking and within a short time became completely dependent upon a wheelchair. There were no other neurological symptoms, including no difficulty in urination or defecation.

On neurologic examination he was alert, cooperative and showed no evidence of an organic mental syndrome. Cranial nerves were intact, except for blindness in the left eye, apparently due to fibrous scarring of the cornea. There was also an internal strabismus of the left eye. Motor examination revealed marked atrophy of all extremities, especially in the intrinsic muscles of the hands. In addition to generalized weakness, he could not walk. The Romberg sign was markedly positive. Heel-to-knee test was done very poorly with the eyes closed and open. There was finger-to-nose ataxia with the eyes closed, but less ataxia with the eyes open. Biceps, triceps, knee and ankle reflexes were all absent. There were no Babinski signs. There was hypoalgesia of both hands and the lower third of the forearm. There was no impairment of pin sensation in the lower extremities. Touch was impaired in the entire body except the face. Position sense was absent in the toes and was markedly impaired in all the digits of the hands. There was bilateral astereognosis. Vibration sense was decreased in both iliac crests and below. Vibration sense was present in the elbows but was decreased in both wrists and hands. In general, there was not much change in his neurological picture since 1953. During the stay at the chronic disease institution, he had been maintained on high protein, low fat, simple carbohydrate diet; vitamin A in doses of 50,000 units a day; calcium lactate 15 grams three times a day; parenteral liver injections weekly; vitamin B_{12}, 50 micrograms weekly and cortisone 25 mg. daily.

Comment: This 45-year old man suffered from the malabsorption syndrome for 15 years. The course has been a stormy one with seven admissions for exacerbations of the gastrointestinal symptoms. He became anemic to the point where he required blood transfusions and also developed pathological fractures due to hypocalcemia. Ten years after the onset of his illness, there ensued a neurological syndrome primarily a myeloradiculo-neuropathy which progressed, despite vigorous therapy with vitamin B_{12} and liver extract, to a point where he was totally incapacitated. He has been maintained on vitamin B_{12}, liver extract and cortisone and has even received a course of folic acid. Nevertheless, there has been no change in his neurological status during the past three years.

Case 2

A 46 year old white woman was admitted for diagnosis and therapy in 1954. Her illness actually extended to infancy, when she had abdominal distension, diarrhea, frequent episodes of vomiting, nausea, fever and respiratory infections. She recalled, as a child, that her mother prepared many special foods for her and remembered eating many bananas. There was a decrease in symptoms until the age of 28 when she had a rather marked exacerbation of her diarrhea and abdominal pain, associated with anemia. In 1945, she was started on liver injections for her anemia and thereafter improved somewhat. She was hospitalized for about one month in 1946 for abdominal distension, diarrhea, severe weakness, anemia and a severe productive cough. Although she was suspected of having tuberculosis at this time, it was never substantiated. In December 1950, she was admitted to another hospital where her presenting complaints were again diarrhea, weakness and weight loss. She had an anemia with a prolonged bleeding time (40 seconds) but normal clotting time; her stools were bulky and foul smelling with a high fat content; oral and intravenous glucose tolerance tests were normal; calcium was 10.8 mg. per cent; serum protein was 5.9 gm. per cent; and she had free hydrochloric acid in her gastric contents. Gastrointestinal series at that time showed "fragmentation of the barium meal." She was treated successfully with vitamin B_{12}, folic acid and crude liver injections. In the summer of 1952, she developed ankle edema and an exacerbation of diarrhea, abdominal distension and pain. She was again admitted and was found to have a flat glucose tolerance curve, a persistent anemia, a hypoproteinemia and again an altered mucosal pattern of the small bowel. She complained of paresthesias of the hands and feet and, although she noted twitching of her fingers, the blood calcium was normal. She had minimal evidences of purpura. She was again treated and did well until February 1953 when, following an episode of "grippe", she was readmitted weighing 80 pounds. During this hospitalization, her calcium was noted to be 8.4 mg. per cent with a normal phosphorus; sigmoidoscopy was negative. She was started on cortisone and maintained on 25 mg. daily. In addition, she received 25 mg. of folic acid daily and crude liver extract, 1 ml. daily. She was also treated with calcium; vitamins A, D and K; and a high protein, simple carbohydrate, low fat diet.

Physical examination revealed a thin, poorly nourished woman with scrawny limbs, a distended abdomen, looking for all the world like a grown-up celiac. There were no pigmentations, no ecchymoses, no eye-ground changes or abnormalities of the tongue. She had no cheilosis. The abdomen was distended and tympanitic. She had 2 plus pitting edema of the lower extremities without sacral edema. She had no clubbing, joint pain or bony tenderness. Neurological examination was unremarkable. She had no Trousseau or Chvostek signs. Tourniquet test was negative. Fluoroscopy revealed no abnormalities of her heart or lungs.

Laboratory analyses: Hemoglobin, 10.9 gm. per cent; hematocrit, 47; RBC, 4.75 million per cu. mm.; MCV, 98; MCH 27; MCHC, 27; platelets, 210,000 per cu. mm.; reticulocytes, 0.6 per cent; white blood cells, 6400 per cu. mm. with 40 per cent segmented polys, 30 per cent lymphocytes, 3 per cent eosinophiles, and 16 per cent monocytes. The blood findings indicated a slight hypochromic but normocytic anemia. Urine examination, sedimentation rate, BUN, fasting blood sugar, plasma carbon dioxide, chloride, sodium, potassium, calcium and phosphorus were normal. Serum protein was 5.69 gm. per cent and the A/G ratio was 2.7/2.4. The prothrombin time was 12.5 seconds (control, 12.5 seconds). Bone marrow examination showed a cellular marrow with an adequate number of megakaryocytes, a marked eosinophilia and normoblastosis, consistent with the recovery phase of a megaloblastic anemia treated with B_{12} or folic acid. Stools were bulky and foul smelling with a high fat content. Serum mucoproteins were 56.6 mg. per cent, polysaccharide of total serum protein was 86 mg. per cent and the polysaccharide mucoprotein ratio was 1.5, all of which were within normal range. Enteric agglutinins were all negative. Oral glucose tolerance test showed a flat curve with no glycosuria. Stool culture revealed *B. coli* and *A. aerogenes*. Vitamin A tolerance test was extremely low with an indeterminable carotene level. Serum cholesterol was 105 mg. per cent; cholesterol esters, 86 mg. per cent. Duodenal drainage with a secretin test showed normal pancreatic function. X-ray of the chest was normal. Barium enema examination showed no abnormality in the esophagus or the stomach. The duodenal bulb was normal except that it appeared somewhat enlarged with thick but regular mucosal folds. The small bowel showed considerable coarsening of the mucosal pattern with moderate dilatation of the lumen, slight segmentation and marked flocculation. Transit time was not grossly disturbed. The changes described were consistent with the clinical diagnosis of non-tropical sprue. Oral cholecystography showed good filling and emptying of the gall bladder with no stones. Skeletal survey revealed a moderated demineralization of visualized bone with no evidence of pseudo-fractures. Calcific densities were noted posterior to the pineal in the skull and probably represented calcification in the choroid plexuses.

The patient had as many as six fatty, foul smelling stools a day. She was started on crude liver extract, menadione, 30 mg. daily of folic acid, vitamin B_{12} (50 micrograms daily), and a high protein, high caloric, low fat diet. On the twenty-second hospital day, she was started on 80 mg. of hydrocortisone daily which was reduced to 60 mg. after one week, but had to be raised since she had an episode of watery diarrhea. This was finally decreased to 40 mg. daily. She was discharged after a hospital stay of six weeks on 30 mg. of folic acid twice weekly, 50 mg. of vitamin B_{12} intravenously, 9 grams of potassium chloride four times a week and supplementary feedings rich in protein. Because of subsequent gastrointestinal symptoms, she was given cortisone. It was felt that her neurological symptoms became worse and when the corticosteroid therapy was discontinued her neurological manifestations improved. A later relapse of sprue necessitated resumption of steroid therapy and it was then given in combination with massive parenteral doses of liver extract and vitamin B_{12}.

On October 18, 1955 she gave a history of a gradual onset of tingling of the hands and the feet since 1951. There were occasional cramps of the toes. These symptoms became less marked but in September 1955, she began to have difficulty in feeling objects, such as buttons and money in her pocket and this had become worse in spite of treatment. She also stated that at times she had burned her fingers and on one occasion a nail in her shoe pierced her foot, but she did not feel it and only later she noticed blood on her stocking. There was also a feeling of not having any sensation about the mouth, and difficulty in tasting things with the tip of her tongue. Her mouth had become very dry and so had the skin of the fingers and soles of the feet. She also mentioned having had dizzy spells which consisted of feelings of being giddy or faint and usually occurred when sitting up rapidly. She complained of urinary frequency and stated that it was uncomfortable to postpone going to the bathroom.

The cranial nerves were entirely intact, except that there was decreased pin sensation throughout the distribution of the trigeminal nerve bilaterally. The tongue appeared smooth. There was no hypoalgesia of the tongue or other mucous membranes. The gait was normal and the Romberg test was negative. There were no abnormal movements. Motor power and tone were normal. There were no fasciculations or atrophy. Finger-to-nose test was done relatively well, but finger-to-finger performance was poor. Heel-to-knee testing was normal. Alternating and discrete fine movements were normal. The biceps, triceps and knee reflexes were all decreased on the left. There were no pathological reflexes. There was decreased sensation to cotton in all the fingers extending to the wrist and all the toes to the ankle. There was position sense loss in the fingers, most marked in the second and third fingers on the right and the second to fifth fingers on the left. There was bilateral astereognosis. Vibratory sense was absent in all her toes except the right big toe and decreased below the ankles. There was a hypoalgesia in the hands and feet. Heat sensation was diminished in the fingers and toes. Two point discrimination was markedly impaired in all digits. There was no extinction or displacement on bilateral spontaneous stimulation.

Comment: This 46 year old woman was particularly interesting because she had apparently had celiac disease in childhood and suffered almost continually from diarrhea. Today, she is a typical adult case of the malabsorption syndrome. Approximately 30 years after the onset of her illness, she developed neurological symptoms in spite of vitamin B_{12}, folic acid and liver extract. The syndrome was mainly that of posterior column involvement and was probably a myeloradiculoneuropathy. When she was given cortisone, there was a relapse of symptoms but this remitted with discontinuance of the hormones. However, later on, corticosteroids were needed because of the gastrointestinal condition and she was given cortisone concomitantly with massive doses of liver extract and vitamin B_{12} which seemed to have protected her from further neurologic damage.

Case 3

A 49 year old man had a history of intermittently recurrent diarrhea for the past eight years. The stools were unformed and foamy, occurring one to two times daily. He was hospitalized in 1936 because of sores on his tongue, one at the tip and another on the left side. These persisted and interfered markedly with his sense of taste. The day after the appearance of these, he developed a severe "rheumatic" pain in the right upper arm and shoulder which gradually spread in the course of three or four days across his upper back to his left shoulder. There was no swelling or limitation of motion. The pain, had, on many occasions, awakened him from sleep. At the same time he began to have a sensation of a cold collar inserted at the base of his neck. This, too, had persisted with some remissions at the time of admission. At night he had experienced severe burning in both hands. For the past week, he complained of numbness in both hands and a lack of a sense of touch. On one occasion, he reached for a coin in his pocket and, thinking he held one, tried to pay for his shine to be surprised when he was told there was no coin in his hand. On many occasions he dropped things because he could not feel them in his grasp. He had not burned his fingers inadvertently. His gait had been steady. There had been no abdominal pain, girdle pain in the abdomen, headache, stiff neck, vomiting, or other neurological symptoms.

He was told he had syphilis six years prior to admission (blood serology was positive on a hospital admission for myocardial infarction). He was treated for one year with weekly injections.

General physical examination revealed a thin, chronically ill, irritable, truculent individual who tended to take offense on unintentional slights. The sensorium was clear. There was bilaterally ptosis of the lids. The right pupil was slightly larger than the left; both reacted to light, the left better than the right. Fundi and visual fields were normal. There was a right central facial weakness. There was slight thickness and slurring of speech. He stumbled over test phrases. Motor power was reduced in both grips, but fair in the proximal segments of the arm. Power in the lower extremities was good. There was slight finger-to-nose ataxia bilaterally, and more marked finger-to-finger ataxia. There was no heel-to-knee ataxia. The deep tendon reflexes in the lower extremities were absent. In the upper extremities, the pectoral reflexes were active, but biceps and triceps reflexes were absent. There were no pathological reflexes. The abdominal reflexes were absent. There was a zone of skin hyperesthesia and hyperalgesia over the C_3-C_5 segments on both sides; most marked about C_4 segment. There was a subjective feeling of tightness associated with spontaneous pains over these zones. There was bilateral astereognosis in the hands; defective joint sense in the fingers. Vibration was absent in the fingers; diminished in the wrist and elbows; markedly impaired in the right toes, less so on the left; slightly diminished above the shins.

Laboratory analyses: hemoglobin, 8.5 gm. per cent; white blood cell count, 4800 per cu. mm.; segmented polys, 53 per cent; lymphocytes, 53 per cent; monocytes, 5 per cent; plasma cells, 1 per cent; eosinophils, 6 per cent; phosphorus, 4.1 mg. per cent; calcium, 12.5 mg. per cent; Wasserman, negative. Janney test: blood sugar #1, 90 mg. per cent; #2, 105; #3, 95; #4, 85; #5, 85 mg. per cent. The spinal fluid was clear and colorless; initial pressure, 80 mm. water; there was no evidence of block; there were three cells per cu. mm.; total protein, 50 mg. per cent; spinal fluid serology (Wassermann) and colloidal gold were negative. A repeat spinal fluid examination revealed a total protein of 81 mg. per cent and the colloidal gold test was still negative, as was the serology test. Gastric analysis revealed free hydrochloric acid. X-rays of the cervical and dorsal spine showed no abnormalities.

It was thought that the patient was suffering from a radiculoneuropathy most likely due to a metabolic disorder such as sprue, but possibly complicated by an old luetic infection. As a result, he was treated with both bismuth and hyperthermia as well as vitamin C injections. He was discharged unimproved.

Comment: This was a 49 year old man who developed neurological signs and symptoms after 18 years of intermittent diarrhea. The picture was complicated by a history of syphilis discovered six years prior to the onset of neurological manifestations. On admission, blood and spinal fluid serology were negative, but the spinal fluid protein was somewhat elevated. He presented the picture of a postero-column syndrome with root pains as well as some dysarthria. There were no Argyll-Robertson pupils. He was treated with heavy metals and hyperthermia but did not respond well. He was discharged unimproved. This case dates back 20 years and it is not known what would have happened if he had been given massive doses of liver extract, vitamin B_{12} and folic acid.

Case 4

A 57 year old man, whose chief complaint was weakness and pain in the left lower extremity of eight months duration, was admitted to The Mount Sinai Hospital in 1953. He had a 25 year history of non-tropical sprue. The patient was in the Navy in World War I, travelling all over Europe, but never in tropical areas. His illness began with the gradual onset of loose stools which were liquid, foul, tan, greasy and frothy. Usually, he had two to four bowel movements per day, but had had as many as 20 per day. He had been in innumerable hospitals and had been diagnosed as suffering from mucous colitis until 1944 when a diagnosis of non-tropical sprue was made. He had been treated with folic acid, vitamin B_{12} and cortisone and had been in relatively good health, but over the long course of his illness he developed a marked generalized osteoporosis, resulting in a severe scoliosis He had no melena, tenesmus, abdominal pain or eructation, but passed much flatus. During the first few years, he fell from his average weight of 154 to 110 pounds, which had been maintained while on a normal diet, except for a low fat content. However, in 1948, he spontaneously developed several large, painful ecchymoses and hematomas over the buttocks, thighs and ankles. At that time he was described as poorly developed, older than his stated years, looking slightly icteric, with marked clubbing, pallor and a distended tympanitic abdomen. He had massive ecchymoses over the lower half of the body. The Chvostek, Trousseau and tourniquet tests were all negative. Laboratory workup revealed the hemoglobin concentration to be 9.9 gm. per cent, the white blood cell count and urine were negative. Platelet count was 190,000 per cu. mm. Vitamin K therapy was started in massive doses and three days later the prothrombin time was 15 seconds (control 15 seconds). Oral glucose tolerance and vitamin A tolerance tests revealed flat curves. The carotene level was 9 μg. per cent, which is strikingly low. Serum protein concentration was 5.3 gm. per cent and the A/G ratio was 3.1/1.4.

On a low fat, high protein diet and vitamin K, he improved quickly and was discharged. He was put on massive doses of vitamin B_{12} and was maintained on 25 micrograms three times a day by mouth. His diet was essentially a low fat one with occasional vitamin B supplements. There were no recurrences of bleeding. His bowel movements varied in frequency from two to four per day. For 13 years prior to admission he had had difficulty in walking, especially up stairs. He had a limp which he attributed to "weakness" which on further questioning was a sharp electric pain in the small of his back when he flexed his leg at the hip.

Physical examination revealed a small thin but pot-bellied white man in no distress. There was obvious marked clubbing of the fingers and toes. His height was 60½ inches, though he claims formerly to have been 62 inches tall. The remainder of the examination was not remarkable except for a distended, soft, doughy, pot-bellied abdomen.

The mental status was normal. There were no cranial nerve abnormalities. He walked with a limp, favoring his left hip and with minimal flexion at the hip. There was weakness of the proximal portion of the left lower extremity. There was weakness of extension, abduction and flexion of the left hip which was accompanied by limitation in passive movements of the hip. Both active and passive movements were painful except for extension at the hip. Neither ankle nor knee reflexes could be elicited, but there were no pathological reflexes. There was slight impairment of vibration sense below L_1 and in the upper extremities.

Laboratory analyses: Hemoglobin ranged between 11–13 gm. per cent; white blood cell count and differential were normal; the urine was negative, except for a trace of albumin; sedimentation rate, 32; BUN, 14 mg. per cent; serum protein, 7 gm. per cent with normal albumin-globulin ratio; calcium, 9.1 mg. per cent; phosphorus, 9.2 mg. per cent; total cholesterol, 117 mg. per cent; prothrombin time, 12 seconds (control, 11 seconds); cephalin flocculation, 1 plus; alkaline phosphatase, 28 King-Armstrong units; stool guaiac examinations were repeatedly negative; pancreatic function studies revealed normal pancreatic function. Gastric analysis revealed a free acid of 40 units and total acid of 75 units after a test meal of alcohol. An oral glucose tolerance test curve was absolutely flat; however, the intravenous glucose tolerance test was normal. A vitamin A tolerance test after intravenous ACTH remained flat. Small bowel series revealed a so-called "deficiency pattern," i.e., from the duodenum to the terminal ileum, the small bowel was dilated with thickened plicae, and fragmentation and segmentation of the barium column. There was no delay in transit time. Spinal fluid was clear and colorless and contained 23 mg. per cent protein and no cells. X-ray of the spine showed compression of the body of the second lumbar vertebra and to a lesser extent the remainder of the lumbar vertebra. There was generalized osteoporosis of the spine and a moderate coxa vara deformity. Because of the progressive story of weakness and the neurological findings it was thought advisable to rule out a lesion of the spinal cord by myelography. A Pantopaque myelogram revealed no evidence of obstruction to the cephalad flow up to the level of the clivus and there was no defect in the Pantopaque column.

Subsequently it was thought that perhaps disease of the hip might be the cause of the weakness and the pain. X-ray pictures of the pelvis revealed a dehiscence through the neck of the left femur which was probably due to osteoporosis and could explain the weakness and the pain. The orthopedic surgeons were consulted and their recommendation was that internal fixation of the neck of the left femur by a bolt was indicated. The patient agreed to undergo operation and has done well since surgery.

Comment: This was a 57 year old man with a 25 year history of gastrointestinal disease most likely due to malabsorption syndrome. He had done rather well on vitamin B_{12}, folic acid and cortisone for many years. He was most interesting in that he developed symptoms of weakness and pain in the left lower extremity which were believed to be due to spinal cord disease, but actually were caused by another complication of the malabsorption syndrome, namely, osteoporosis with a complicating pathological fracture of the neck of the femur. Following surgery, he did well.

OTHER CASES

Table I is a compilation of neurologic manifestations of the remaining 45 patients. These manifestations fall into three groups. Group A includes patients with neurologic signs and symptoms such as paresthesias, reflex changes and/or sensory abnormalities (21 patients). Group B is comprised of those with manifestations of tetany (16 patients). Group C is made up of patients with combined forms of both neurologic abnormalities and tetany (8 patients).

In Group A there were 21 patients with some neurologic involvement. Thirteen had complaints of paresthesias of the fingers and toes. These were described as numbness, pin and needles sensation and/or burning feeling. None had objective neurological findings. Their ages ranged from 24 to 60; the duration of illness, from one to 25 years. Nine patients had severe anemia, but five had normal blood counts (one patient's blood count was not available). One of the 13 patients was said to be a possible diabetic and should be perhaps excluded from this series. Moreover, two were reported to have positive serologic tests for syphilis. An additional four patients had no neurologic symptoms, but had decreased or absent deep tendon reflexes of the lower extremities. One of these patients also had a positive serological test for syphilis. Another patient had a "cerebrovascular accident" at the age of 57 and should be omitted since this is most likely not related to the malabsorption syndrome. There were three additional patients who had both sensory symptoms and objective neurologic findings. One of these, a 65 year old man, had had bowel dysfunction for three years, was reported to have 6 gm. per cent hemoglobin and 2.2 million red blood cells per cu. mm.; another was a 37 year old man who suffered from gastro-intestinal symptoms for one year and had a normal blood count and hemoglobin; the third patient is the only one who had definite spinal cord disease in that she developed a Brown-Sequard syndrome which spontaneously cleared in a few weeks. Details were not available and it is possible that there might have been a coincidental occurrence of an acute attack of multiple sclerosis.

In Group B there were 16 patients who had tetany or signs of nerve irritabil-

TABLE I

Patient No.	Sex	Age	Duration Malabsorption Syndrome, Years	Anemia	Paresthesias	Reflex and/or Sensory Changes	Tetany
Group A 6	M	18	21	None	Present	None	None
9	F	47	2	Present	Present	None*	None
11	M	26	1	Present	Present	None	None
12	M	65	3	Present	Present	Present	None
18	F	47	4	Present	None	Present	None
20	M	49	2	Present	None	Present*	None
23	F	60	1	Unknown	Present	None	None
24	F	55	1	Present	Present	None	None
26	F	22	1	Present	Present	None*	None
27	F	24	1	Present	Present	None	None
28	F	37	1	None	Present	Present	None
33	M	34	4	None	None	Present	None
38	M	57	2	None	Present	None†	None
40	F	77	6	Present	None	Present	None
42	M	21	13	Present	None	Present‡	None
43	F	40	25	Present	Present	None	None
44	M	72	17	Present	Present	None	None
46	F	48	6	Present	Present	None	None
47	M	28	1½	None	Present	None	None
48	F	45	28	None	Present	None	None
5	F	28	17	Present	Present	Present	None
Group B 7	M	50	2	Present	None	None	Present
8	M	16	1	None	None	None	Present
10	F	55	13	Present	None	None	Present
16	M	56	1	None	None	None	Present
17	F	34	1	None	None	None	Present
21	M	45	2	None	None	None	Present
22	F	28	1	None	None	None	Present
25	F	68	15	None	None	None	Present
29	F	68	3	None	None	None	Present
30	F	37	1	None	None	None	Present
31	F	60	¼	Present	None	None	Present
32	F	65	3	None	None	None	Present
34	F	30	10	Unknown	None	None	Present
35	F	41	19	Present	None	None	Present
37	F	42	12	Present	None	None	Present
49	F	59	¾	None	None	None	Present
Group C 13	F	55	3	Present	None	Present	Present
14	F	47	11	None	Present	None	Present
15	F	34	12	None	Present	None	Present
19	F	28	3	Present	None	Present	Present
36	F	32	4	Present	Present	None	Present
39	F	59	3	Present	None	Present	Present
41	F	47	11	Present	None	Present	Present
45	F	42	16	Present	Present	None	Present

---

* Positive serological test for syphilis.

† Co-existent diabetes.

‡ Patient had cerebral lesion due to vascular disease.

ity (carpopedal spasm or positive Chvostek and Trousseau signs). Their ages ranged from 16 to 68. One patient had been ill for only three months and the patient who had been ill the longest time suffered for 19 years. None had any other manifestations of abnormalities of the peripheral or central nervous system.

Group C consisted of 8 patients, all of whom had tetany and half of whom had neurologic symptoms; the remaining four had decreased or absent deep tendon reflexes of the lower extremities. Two patients were found to have diminished sensation to vibration also and one patient had a hypoalgesia and loss of position sense of the toes. These patients were between the ages of 28 and 59 and had been ill from three to 16 years. All but two of them had a severe anemia.

DISCUSSION

The studies reported in this paper indicate that neurologic manifestations are not too rare in the malabsorption syndrome. This is in contradistinction to most writers on the subject. Thaysen (7) had mentioned paresthesias and slight but rare objective changes and was convinced that neurologic abnormalities were not conspicuous. He took strong issue with Reed and Ash (8) and Reed and Wyckoff (9), who collected cases of "atypical sprue" with neurologic complications and who felt that sprue, Addison's anemia and subacute combined degeneration of the cord were expressions of the same disease. In the latter's patients, paresthesias, sensory disturbances and reflex changes were present, and there seems to be no doubt of a peripheral radicular neuropathy, although myelopathy may be questioned. Snell (10) reported the experiences of the Mayo Clinic and described 32 cases, three of whom were considered to have subacute degeneration of the cord. Spies (11) in appraising the results of vitamin B_{12} therapy in tropical sprue mentioned three cases with combined system disease; two of them responded to B_{12} and a third to liver extract. However, there were no detailed reports of any of these cases. Manson-Bahr (12) stated that in severe anemia neurological symptoms such as paresthesia (tingling and numbness) were frequently seen; serious diseases of the nervous system were absent in contradistinction to Addisonian anemia. However, there was mention of a patient with paresthesias, ataxia, loss of ankle and knee reflexes which improved with vitamin B_1 injections and there were two additional cases of subacute combined degeneration of the cord accompanying a sprue anemia, one of whom ran an acute rapidly progressive course and proved to be terminal. Cord symptoms manifested themselves in ataxia of the limbs, ankle clonus and positive Babinski signs. In contrast, Lindsay (13) reported a 15 year follow-up in 37 cases of nontropical sprue with no mention of neurologic involvement. In 1947, Adlersberg and Schein (14) reported on the clinical and pathological observations in a group of 40 patients manifesting the sprue syndrome. In this series, outspoken organic disease of the central nervous system was not encountered. The paresthetic phenomenon could always be ascribed to the anemia. Neuromuscular hyperirritability could likewise be explained in every instance by hypocalcemia. In a symposium on sprue at the Second International Congress of Internal Medicine in London, 1952, there was no mention of any serious neurological disorders although there was passing reference to symptoms of vitamin B deficiency. Cooke, Penney and Hawkes (15) reviewed 100 cases of idiopathic steatorrhea and reported only two cases of absent reflexes, abnormal plantar response and absent vibration sense. A few patients had diminished reflexes which appeared to be the result of electrolyte disturbances rather than manifestations of peripheral neuritis; these signs disappeared with the improvement of the general condition of the patients. Davidson and Girdwood (16) in reporting the effect of folic acid on six patients, described two who had idiopathic "diarrhea." Their case 4 presented no neurologic symptoms until she was given 20 mg. of folic acid for 20 days. The patient then began to feel pins and needles in both arms and legs. At this time, the red cell count was four million cells per cu. mm. Folic acid was discontinued, but the paresthesias became worse; 14 days later, power was lost in the arms and legs, and the ankle reflexes were weak. Triceps and brachioradialis reflexes were absent. The biceps reflex was normal as well as the plantar response. There was a distal hyperalgesia in the legs, more so than in the arms and there was a tactile hypoalgesia in the lateral aspects of the lower two-thirds of both legs. The patient was given liver extract, thiamine, riboflavin and nicotinic acid with improvement of the neurological signs. Their case 3, age 61, had been successfully treated with folic acid six months previously for a severe megaloblastic anemia. For an additional four months she was well without therapy, but then developed paresthesias of the hands and the feet, ataxia, diarrhea and a blood count of four million (previously five million) per cu. mm. There was muscular weakness and wasting, hyperalgesia on pressure of muscles and nerve trunks and loss of reflexes in both arms and legs. There was pronounced impairment of fat absorption. Folic acid and thiamine did not help over a five month period and the patient progressed to profound weakness with complete loss of all deep tendon reflexes, severe sensory loss and ataxia. At no time was an extensor plantar response found and the red cell count never fell below four million per cu. mm. They then administered parenteral liver injections and the patient had a good remission.

In the first mentioned case, folic acid may have temporarily worsened the neurological condition; in the second case, it did not help, but may have perpetuated the abnormality. In our own case 1, the neurologic problems began prior to any folic acid administration and were not made worse when this substance was given. Adlersberg (17) in previously discussing this case mentioned that folic acid medication was contraindicated in idiopathic sprue in the presence of lesions of the central nervous system. He felt that increased doses of concentrated liver extract and vitamin B_{12} and improvement of the general condition may lead to regression and disappearance of the mild manifestations of neuropathy. The severe pseudotabes of this particular patient, however, was irreversible despite marked improvement of his general status after daily parenteral administration of very large doses of concentrated liver extract, vitamin B_{12} and iron. This patient dramatically demonstrates that although most of the neurologic manifestations in the malabsorption syndrome are minor and are related to anemia, a progressively crippling myeloradiculoneuropathy (a pseudotabes) can ensue which is refractory to all known medication. This man has not walked in five years and is institutionalized at a hospital for chronic disease. This is a challenging problem since we do not know what factors determine which patient will develop disabling neurologic sequellae. It does not seem to be related to the duration of illness, the age of onset, the presence of tetany or the severity of the anemia.

Excluding patient 3 who had syphilis, this patient and patient 2 are the only two out of 94 patients with severe neurologic impairment. There is a possibility that they suffered from two neurologic entities not related to the malabsorption syndrome, and that the relationship is coincidental. Until we learn more about the pathophysiology of the malabsorption syndrome, especially with regard to its effect on the nervous system, this conservative attitude is advisable. At this time we can only assume a causal relationship between the malabsorption syndrome and the neurologic manifestations.

A major question which cannot be resolved is the effect of an anemia on neurologic manifestations. According to our cases, the paresthesias, diminished to absent reflexes, and the sensory abnormalities seem related to low blood hemoglobin and cell counts. However, it was not possible to correlate the neurologic abnormalities with the time, duration or severity of the anemia. Nevertheless, we have eight patients with neurologic abnormalities but normal blood values (Thaysen (7) also mentioned normal values in patients with paresthesias). These cases might indicate a malabsorption of some factor or factors which are essential for intactness of nerve tissue. Three of our cases reported in detail had periods of anemia, but the fourth was never anemic. It is true that this latter case is complicated by a past history of syphilis. However, the syphilis was treated, apparently adequately, since on the admission described there was no laboratory evidence of lues. One wonders, however, if such an illness as syphilis might predispose the development of neurologic sequellae if a malabsorption syndrome ensues.

The effect of corticosteroid therapy on the gastro-intestinal manifestations of the malabsorption syndrome has been quite gratifying. Concerning neurologic sequellae, it was felt in our case 2 that these signs and symptoms had become worse. Adlersberg (17) had previously mentioned that degenerative neurologic manifestations, not too frequently encountered in sprue, were enhanced by corticosteroid therapy and were improved by its discontinuance. Complete relapse of sprue necessitated resumption of steroid therapy. It was then given in combination with massive parenteral doses of liver extract and vitamin B_{12} (a procedure which is now used in all patients with central nervous system involvement requiring corticosteroid therapy). This patient (our case 2) is particularly interesting because it is the only example we have of a case of celiac disease in childhood progressing to the full blown adult picture of the malabsorption syndrome who, in addition, has developed marked neurologic involvement. At present, her neurologic status is quiescent although she is currently being given small doses of corticosteroids as well as massive doses of vitamin B_{12}. We do not feel that corticosteroids are too dangerous with respect to neurologic manifestations in patients with a malabsorption syndrome, since we have 28 other patients who take steroids and who have never developed any neurologic abnormalities. Moreover, ACTH has been given to patients suffering from the so-called Guillan-Barre syndrome (18) with perhaps some benefit in the early cases. Also, steroids have been advocated in Bell's palsy (19) and are considered to be efficaceous in this particular neuropathy. At any rate, it does not seem that steroids can significantly complicate the neurologic picture.

Of the 49 cases presented, 27 had manifestations of nerve irritability, most likely due to decreased serum calcium because of malabsorption. This has been well discussed in the literature. Eleven of our cases had both objective nervous system abnormalities and tetany. It was felt that these cases showed two separate phenomena, since when tetany occurs in other conditions, definite objective sensory phenomena or reflex changes are rarely, if ever, found (20). Interestingly, the remaining 38 patients had either tetany or some other neurologic manifestation. It was not possible to explain this apparent mutual exclusion. Moreover, there was one patient in our series who entered the hospital seriously ill with tetany, who had a convulsion and died. An almost identical case was described by Pessera (21) and in his particular patient there were no pathologic changes in the brain.

THERAPEUTIC ASPECTS

Anemia. The treatment of the patient with macrocytic anemia is high doses of vitamin B_{12}, up to 1000 micrograms two or three times a week or even daily. However, if there is a microcytic anemia, iron by mouth or, if necessary, intravenously is administered; and also blood transfusions, if indicated.

Tetany. The management of tetany consists of oral doses of calcium lactate or calcium gluconate. We usually administer 15 grains three times a day. Ammonium chloride also has been found to be efficaceous.

Even if the patient does not present evidence of anemia, we nevertheless maintain him on adequate doses of vitamin B_{12}. Whether one should give folic acid or not is a rather controversial subject. However, it is our impression that this substance might be helpful; but, if it is to be given, it should be done with concomitant high doses of vitamin B_{12} and thiamine.

Corticosteroids may be indicated in the general treatment of the malabsorption syndrome and, if a patient is developing early signs and symptoms of neurological involvement, we feel that they ought to be given in combination with massive parenteral doses of liver extract and vitamin B_{12}.

SUMMARY AND CONCLUSIONS

A study of the neurologic manifestations of the malabsorption syndrome in 94 patients is presented. Forty-nine patients (52 per cent) had signs and symptoms of nervous system involvement; 21 had some significant abnormality of the nervous system which was apparently related to anemia. However, neurologic sequellae were noted in eight patients who never were anemic. Sixteen patients had evidence of tetany; eight patients had combination of both nervous system involvement and tetany. Four patients are reported in detail, three of whom had marked involvement of the nervous system, primarily a myeloradiculoneuropathy. Since one of the latter had had syphilis, only two of 94 patients had severe manifestations of nervous system disease which could be reasonably attributed wholely to the malabsorption syndrome.

There were sixteen patients who only suffered from tetany and twenty-two other patients with signs of neurologic involvement such as paresthesias, absent reflexes, sensory abnormalities, without tetany. The reason for this mutual exclusion is not clear.

The therapeutic management of patients suffering from the malabsorption syndrome with neurologic manifestations is discussed.

ACKNOWLEDGMENT

The author wishes to express his appreciation to Dr. David Adlersberg for reviewing this paper and his valuable and helpful suggestions. I also wish to acknowledge secretarial help of Mrs. Isabel Hall.

REFERENCES

1. Parsons, L. F.: Celiac Disease. Am. J. Dis. Child., 43: 1293, 1932.
2. Haas, S. V., and Haas, M. P.: Management of Celiac Disease. J. B. Lippincott and Co., Phila. 1951.
3. Allibone, E. C.: The Treatment of Celiac Disease with Vitamin B Complex and Liver Extract. Proc. Roy. Soc. Med., 39: 700, 1946.
4. Grodwohl, R. B. H.: Clinical Tropical Medicine. C. V. Mosby, St. Louis, 1951.
5. Mackaie, F. P., and Fairley, N. H.: The Morbid Anatomy of Sprue. Ind. J. Med. Research, 16: 749, 1929.
6. Rodriguez-Molina, R.: Fundamental Concepts in the Diagnosis of Sprue. Ann. Int. Med., 40: 33, 1954.
7. Thaysen, T. E. H.: Non-Tropical Sprue. Oxford University Press, London, 1932.
8. Reed, A., and Ash, J. E.: Atypical Sprue. Arch. Int. Med., 40: 786, 1927.
9. Reed, A., and Wycoff, H. A.: The Common Picture of Sprue, Pernicious Anemia and Combined Degeneration. Am. J. Trop. Med., 6: 221, 1926.
10. Snell, A. M.: Tropical and Non-Tropical Sprue, Their Probable Interrelationship. Ann. Int. Med., 12: 1632, 1939.
11. Spies, T. D., Suarez, R. M., Lopez, G. G., Milanes, F., Stone, R. S., Toca, R. L., Aramburu, T., and Kartus, S.: Tentative Appraisal of Vitamin B_{12} as a Therapeutic Agent. J. A. M. A., 139: 521, 1949.
12. Manson-Bahr, P.: The Dysenteric Disorders. Williams and Wilkins, Baltimore, 1943.
13. Lindsay, M. K., Nordin, B. E., and Norman, A. P.: Late Prognosis in Celiac Disease, Brit. Med. J., 4957: 14, 1956.
14. Adlersberg, D., and Schein, J.: Clinical and Pathologic Studies in Sprue. J. A. M. A., 134: 1459, 1947.
15. Cooke, W. T., Peeney, A. L. P., and Hawkins, C. F.: Symptoms, Signs and Diagnostic Features of Idiopathic Steatorrhea. Quart. J. Med. New Series, 22: 59, 1953.
16. Davidson, L. S. P., and Girdwood, R. H.: The Imbalance of Vitamins with Particular Reference to Folic Acid. Lancet, 1: 360, 1948.
17. Adlersberg, D.: Problems of Management of Idiopathic Sprue. N. Y. State J. Med., 55: 3575, 1955.
18. Crozier, R. E., and Anley, A. B.: The Guillian-Barré Syndrome. N. Eng. J. Med., 252: 83, 1955.
19. Rothendler, H. H.: Bell's Palsy Treated with Cortisone. Am. J. Med. Sci., 225: 358, 1953.
20. Wilson, S. A. K.: Neurology. Williams and Wilkins, Baltimore, 1955.
21. Passera, A. E.: Non-tropical sprue. N. Y. State J. Med., 54: 1674, 1954.

OSSEOUS CHANGES AND FRACTURES IN THE MALABSORPTION SYNDROME

JOEL HARTLEY, M.D.
New York, N. Y.

The insidious development of bone pains and/or fractures without trauma in patients who have inadequate intestinal absorption because of sprue has brought to our attention the problem of bone changes and orthopedic management of these patients. The changes have been known and reported in the literature (1–14) but deserve emphasis.

It has been established that patients suffering from idiopathic steatorrhoea, and other causes of malabsorption, suffer defects in proper absorption of fats, particularly the saturated fats. Associated difficulty in absorption of the fat-soluble vitamins causes hypovitaminosis D and has a deleterious effect on maintenance of proper mineralization of the bones. Malabsorption of vitamin D prevents proper absorption of calcium (15) and causes osteomalacia, mild degrees of which are commonly seen in patients with the malabsorption syndrome (Figs. 1 and 2). Roentgenograms for intestinal studies frequently disclose asymptomatic osteomalacia of the spine as an incidental finding. In cases other than sprue inadequate intake of vitamin D or its faulty utilization will produce the same clinical picture. Patients with "incomplete sprue" may manifest little or no diarrhea and yet develop osteomalacia (16, 17).

The distinction between osteomalacia and osteoporosis must be kept clearly in mind (18, 19). Osteomalacia in general, whether associated with sprue or not, is an adult form of rickets resulting from a lack of vitamin D and sunshine. This in turn prevents proper absorption of calcium and impairs calcium salt deposition in the bone matrix (osteoid). Both the serum calcium and serum phosphorus concentrations may be normal or low, while the blood alkaline phosphatase concentration is usually elevated. In regions where proper diet and exposure to sunshine exists, osteomalacia from deficiencies of these two factors is quite infrequent. However, in these regions osteomalacia may be seen as a secondary effect in conditions where there is malabsorption of the fat-soluble vitamin D in the intestinal tract and/or a lack of adequate food intake (20).

Osteoporosis, on the other hand, is a state of deossification, an actual thinning of bone trabeculae due to a defect in protein matrix. It is a disease of tissue metabolism and not of calcium metabolism. Adequate ingestion, absorption and transportation of vitamin D and minerals may be present but osteoporosis, nevertheless will exist. Serum calcium, phosphorus and alkaline phosphatase levels are relatively normal (18). It is seen mostly in post-menopausal, disuse, post-traumatic and senile states and in Cushing's syndrome. It occurs less commonly in other conditions such as scurvy and acromegaly, or it may be

---

From the Department of Orthopedic Surgery, The Mount Sinai Hospital, New York, N. Y.

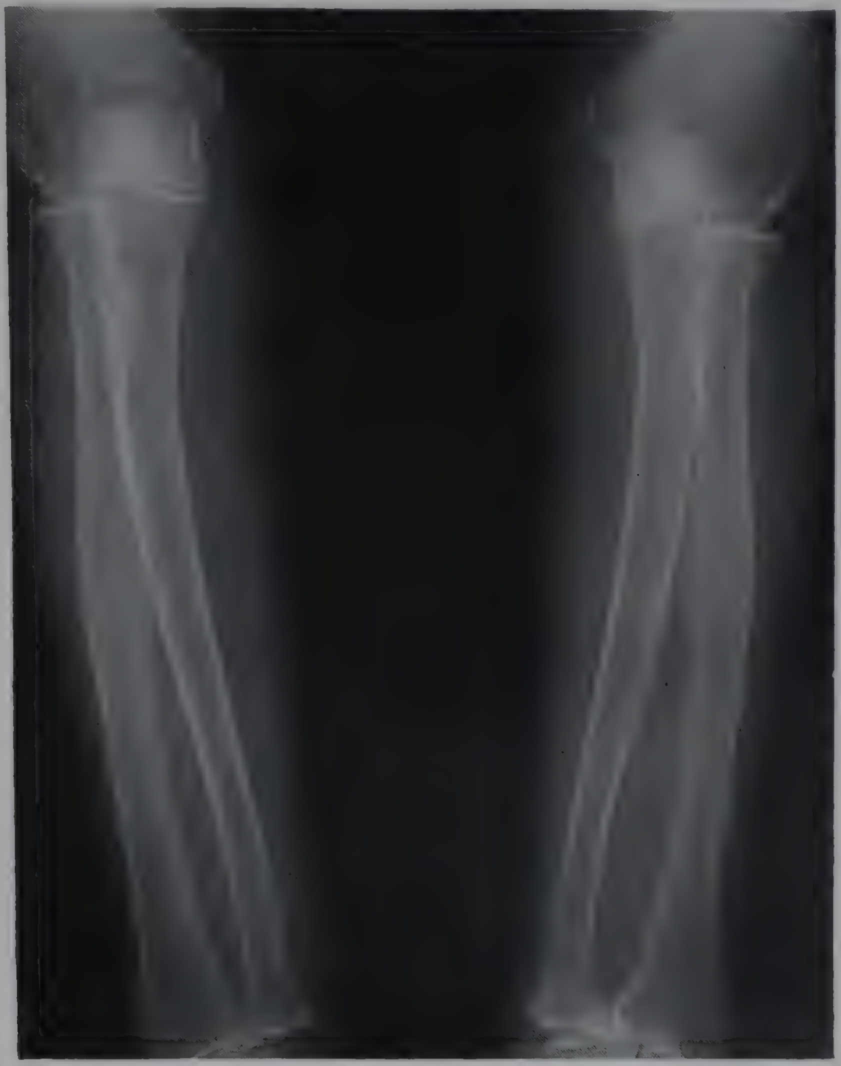


FIG. 1. Incidental finding of osteomalacia in a case of sprue without skeletal symptoms. Forearm bones shown.

idiopathic. Osteporosis produces roentgenologic changes in the vertebrae and pelvis, and less frequently in the skull and the extremities.

Progressive softening of the bone from osteomalacia alone or osteomalacia plus osteoporosis results in a weakened skeletal supporting structure which may not sustain the mechanical requirements of ordinary living. An interruption or collapse of osseous structure may develop without external trauma. So-called pseudo-fractures of the pubis are most common. Next in frequency are lesions of the femoral neck, axillary border of the scapula, and ribs (21).

CASE REPORTS

Three instances of slowly developing osteomalacia in known cases of primary sprue were encountered in which osseous discontinuity occurred. A fourth instance appeared in a patient who had a subtotal gastrectomy two years previously.

Case 1

P. S., a 57-year old, white, Jewish salesman, gave a history of diarrhea in World War I, but his first symptoms of sprue appeared in 1931. In 1948 the diagnosis of sprue was definitely established on the basis of laboratory tests at The Mount Sinai Hospital, but it is reasonable to suppose that the diarrhea in World War I represented idiopathic steatorrhoea.

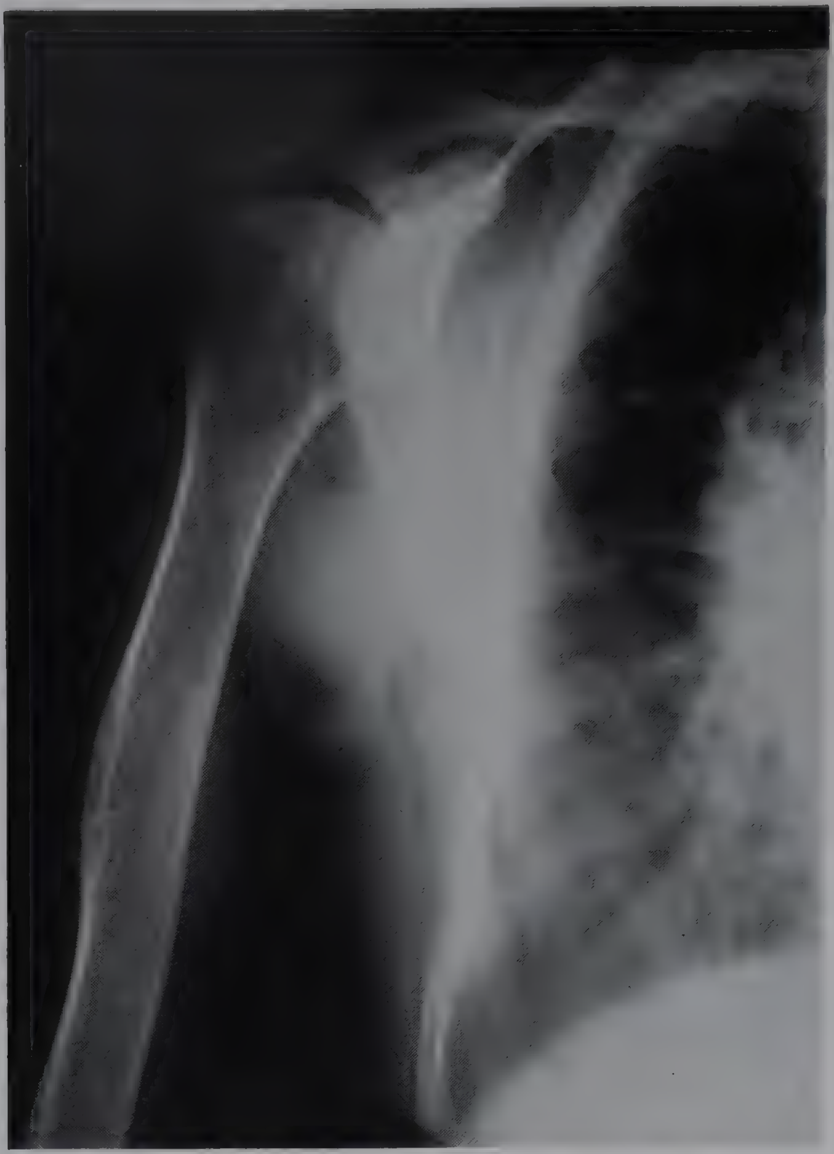


FIG. 2. Humerus of same case as in Fig. 1

Because of an unsatisfactory response to therapy, he was treated with 80 mg. of hydrocortisone daily, which was effective in relieving his symptoms of sprue. Later, the dose was reduced to 40 mg. daily and maintained at that level. After 18 months of corticosteroid therapy he was readmitted to the hospital (April 5, 1955) because of pain and weakness of his left lower extremity.

The positive physical findings consisted of a limp due to pain and weakness of the left lower extremity, and a shuffling gait. Neurologic examination disclosed diminished biceps reflexes bilaterally, absent left cremasteric reflex and diminished vibratory sensation of feet and the fourth and fifth fingers of the hands. Motions of the left hip were limited and painful. Mild diffuse spinal tenderness was present. Serum calcium and phosphorus values were both low and the blood alkaline phosphatase was elevated. The lowest serum calcium concentration was 7.8 mg. per cent and the lowest serum phosphorus concentration was 1.3 mg. per cent. The highest blood alkaline phosphatase was 11 King-Armstrong units. During therapy the serum calcium and phosphorus concentrations returned to normal. The blood alkaline phosphatase was then 10 King-Armstrong units.

X-ray studies revealed generalized deossification of the bones, fish-shaped intervertebral spaces, a pseudo-fracture through the neck of the left femur (Fig. 3), early degenerative changes of both hips, transitional fifth lumbar vertebra, slight compression of the body of L_4 and an old healed fracture of the right clavicle.

Internal fixation was performed by means of a Lippmann corkscrew bolt (Fig. 4). The patient's post-operative course was characterized by dramatic improvement of his left lower

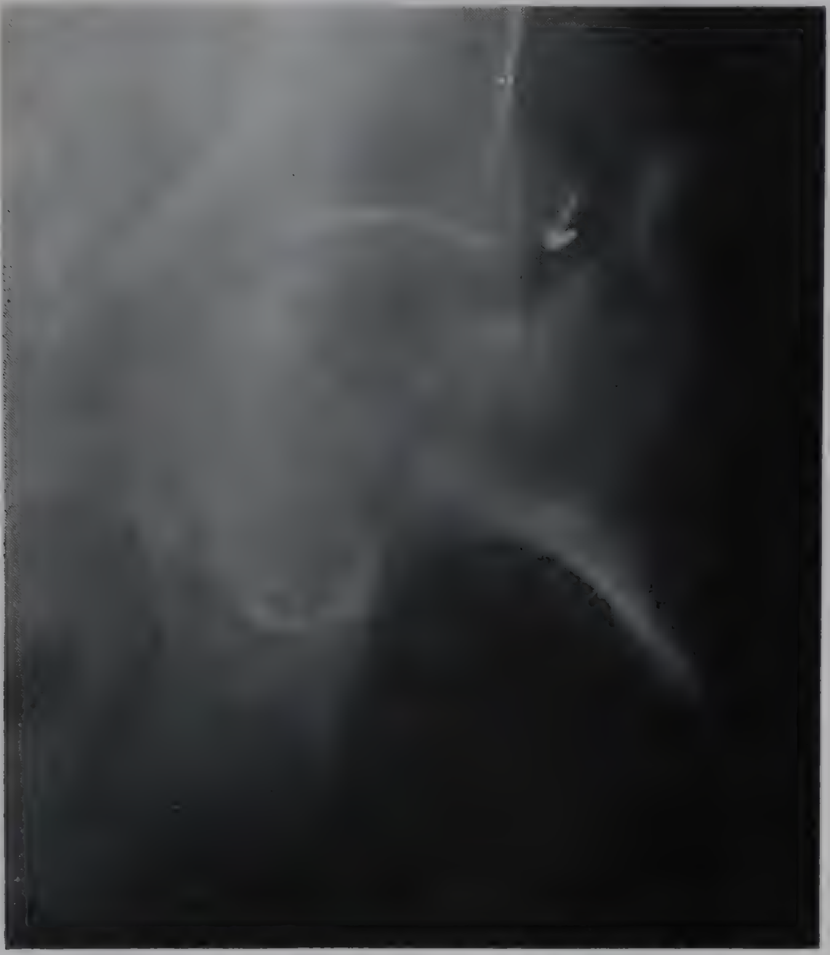


FIG. 3. Case 1, osseous discontinuity in neck of left femur in a case of malabsorption syndrome (sprue) treated with corticosteroid.

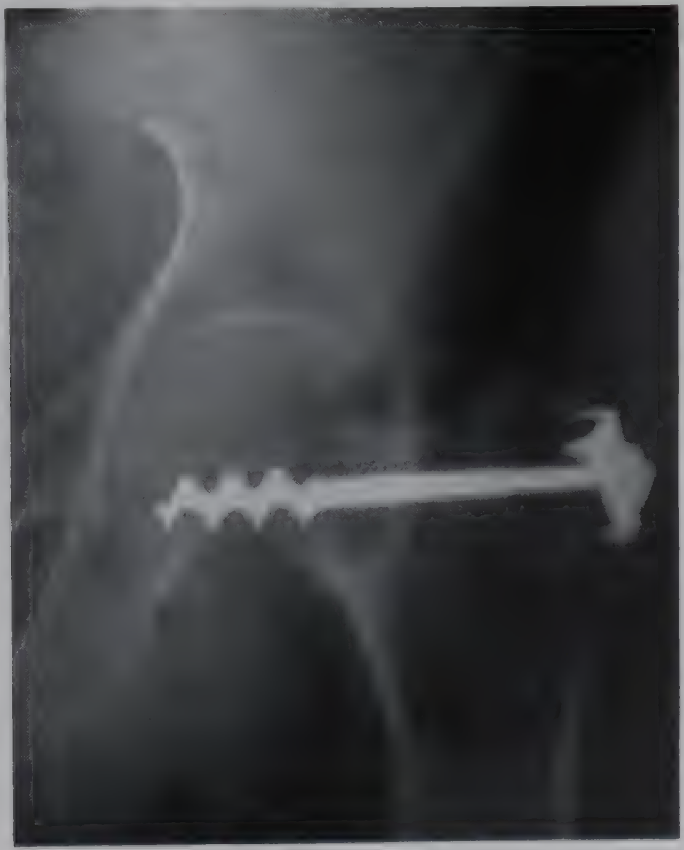


FIG. 4. Case 1, after internal fixation with Lippmann corkscrew bolt.

extremity pain. His gait became painless and normal appearing. Androgen-estrogen therapy, high protein diet, vitamins and calcium were administered. Two years after the operation the patient was still doing well. He was still on small doses of corticosteroids and was in remission as regards his sprue.

Comment: A patient with sprue of long duration treated with corticosteroids is presented. Studies disclosed severe osteomalacia and superimposed osteoporosis which resulted in a fissure fracture of the neck of the femur and a compression fracture of the fourth lumbar vertebra. Internal fixation of the fracture was performed with excellent result.

Case 2

C. L., a 62-year old, Puerto Rican female, was a known case of primary malabsorption syndrome (idiopathic sprue) associated with a macrocytic anemia (August 1955). She improved under treatment at The Mount Sinai Hospital with folic acid and vitamin B_{12}. The macrocytic anemia improved and microcytic anemia appeared, but there was no change in the diarrhea. This remained refractory to treatment until prednisone was added to her regimen. Lowest values of serum calcium and phosphorus concentrations were 9.4 mg. per cent and 2.8 mg. per cent, respectively. The blood alkaline phosphatase level was 22 King-Armstrong units. After clinical improvement was manifest, the values of serum calcium and phosphorus became normal. Her blood alkaline phosphatase level was then 8.8 King-Armstrong units.

On February 28, 1956, seven months after corticosteroid treatment was started, she fell and developed pain in the left hip. X-rays revealed generalized deossification, a valgus type

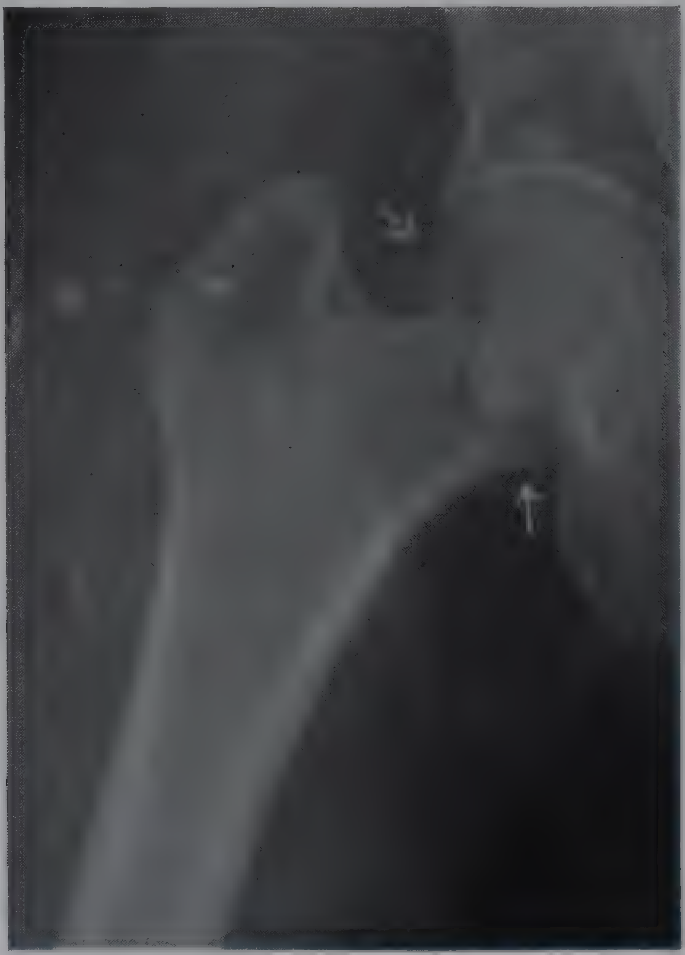


FIG. 5. Case 2, complete fracture, neck of femur in a case of malabsorption syndrome (sprue) with osteomalacia.

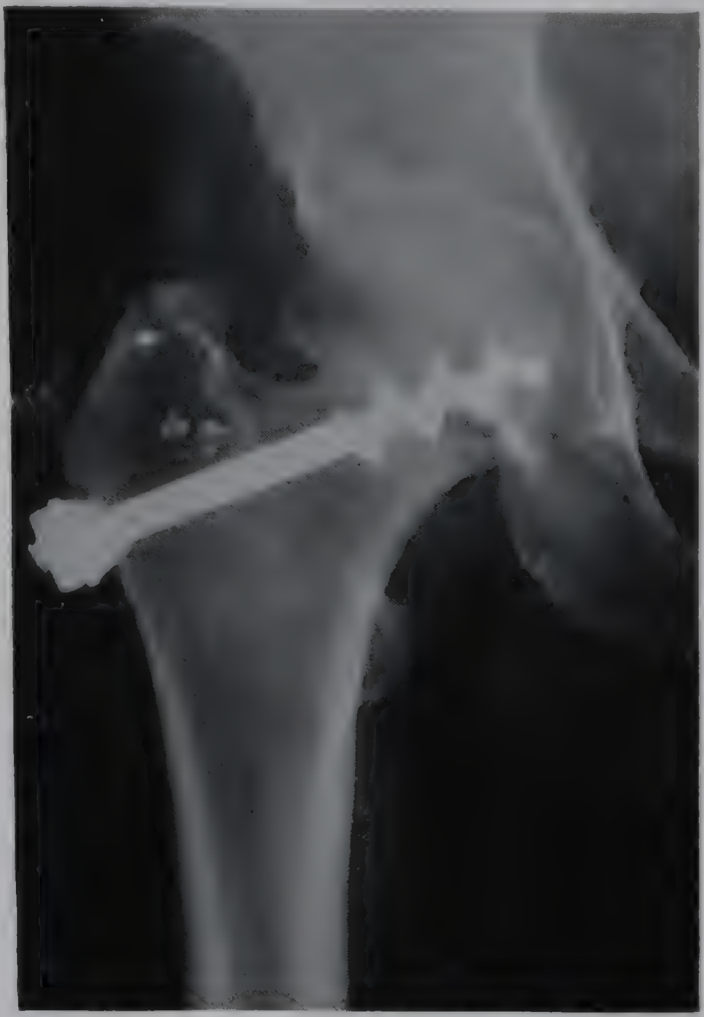


FIG. 6. Case 2, compression of body of twelfth dorsal vertebra.

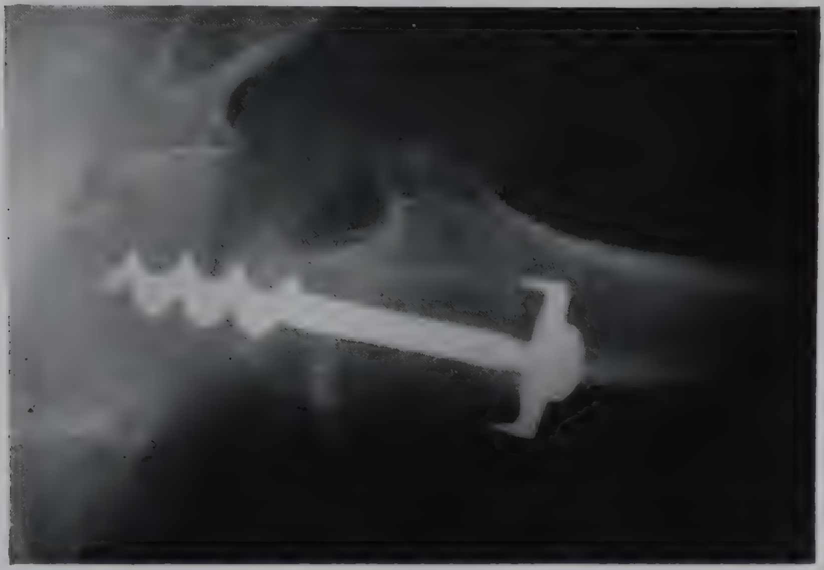


FIG. 7. Case 2, after internal fixation with Lippmann corkscrew bolt.

fracture of the neck of the left femur (Fig. 5) and compression of the body of the twelfth dorsal vertebra (Fig. 6). Internal fixation by means of a Lippmann corkscrew bolt was performed (Figs. 7 and 8). Her post-operative course was uneventful. Ambulation was started promptly, weight bearing initiated three weeks later and the pain in her hip disappeared. However, pain in the back persisted. Continued small doses of prednisone were required for relief of her sprue symptoms.

Comment: A patient with idiopathic sprue who was refractory to usual treatment, but relieved by prednisone, is presented. Severe osteomalacia and osteoporosis resulted in fracture of the neck of the left femur and a compression fracture of the twelfth dorsal vertebra. Internal fixation of the hip fracture was performed with improvement.

Case 3

N. F., a 43-year old, white male, was born in Italy and came to New York City at the age of 19. He was well until 1942, when he developed severe, watery, non-bloody diarrhea, with foul smelling stools, vomiting, weakness, anorexia and weight loss. Since that time, he has had intermittent attacks with exacerbation and remissions. In 1948, he suffered a fracture of the left hip and was treated at another hospital. He was admitted to other hospitals a number of times before coming to The Mount Sinai Hospital on December 8, 1953. His first ex-

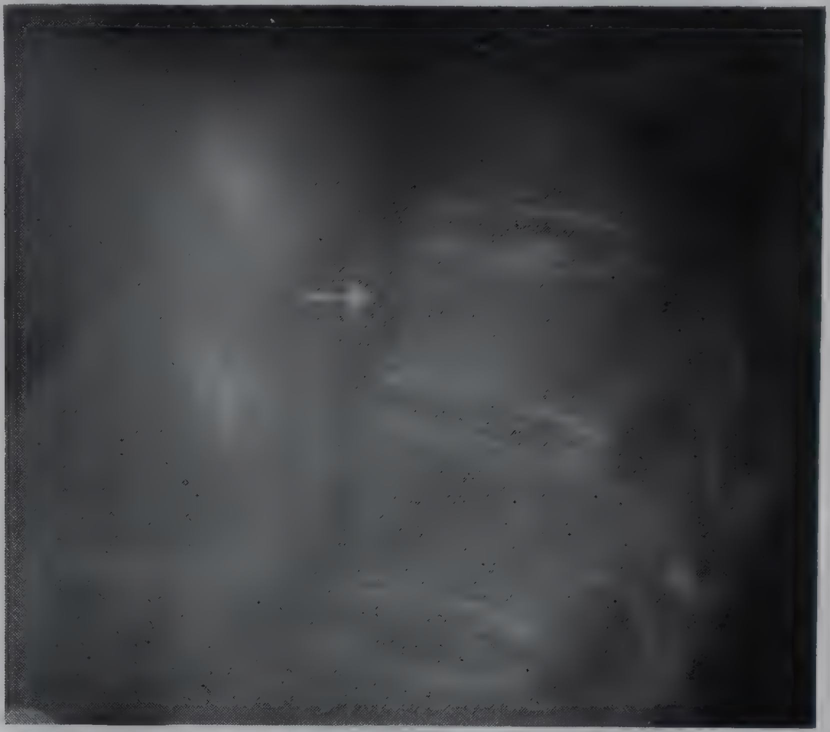


FIG. 8. Case 2, lateral view.

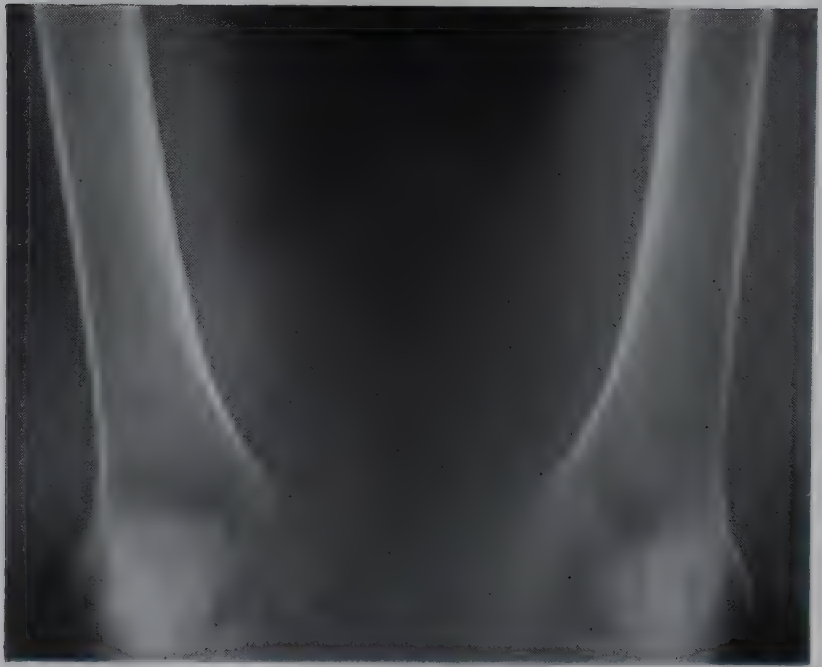


FIG. 9. Case 3. Osteomalacia of femora, malabsorption syndrome (sprue) of long standing.

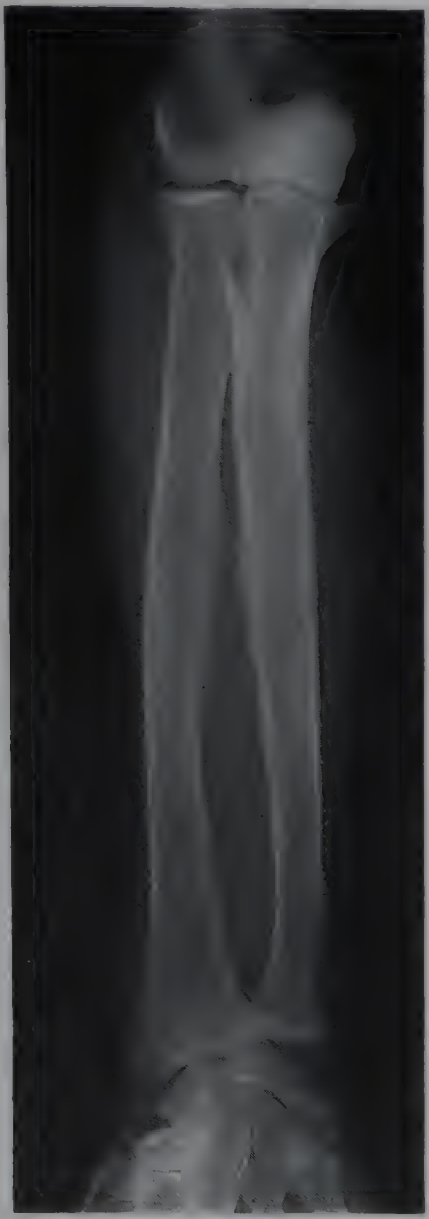


FIG. 10. Case 3. Osteomalacia of forearm bones.

amination at The Mount Sinai Hospital revealed him to be an emaciated, chronically ill, white male of very short stature with marked kyphoscoliosis who was unable to walk unassisted. Neurologic changes indicative of posterior column disease were present. Detailed studies indicated the presence of non-tropical sprue with hyperchromic anemia. Blood chemical studies revealed the lowest value of serum calcium to be 5.9 mg. per cent, serum phosphorus 2.7 mg. per cent. The highest value of blood alkaline phosphatase was 24 King-Armstrong units. For over one year prior to admission he received injections of ACTH. A roentgenologic bone survey revealed a marked degree of generalized demineralization (Figs. 9 and 10). The vertebrae had a bioconcave appearance (Fig. 11). There were old healed fractures of the right scapula and right clavicle (Fig. 12). There was also a healed fracture of the left hip. He improved under medical treatment consisting of vitamin B_{12}, intravenous iron and 80 mg. of hydrocortisone daily. Blood serum calcium increased to 8.6 mg. per cent; serum phosphorus to 4.5 mg. per cent. Blood alkaline phosphatase decreased to 18 King-Armstrong units. Sulkowich test of urine was negative. He was discharged on September 9, 1954, ten months after admission, very much improved and was continued on 40 mg. of hydrocortisone daily. However, his neurologic status did not change. He was then transferred to a convalescent institution.

On November 13, 1956, he was re-admitted to The Mount Sinai Hospital because of increasing numbness of the hands and feet. Examination revealed posterior column disease and peripheral nerve involvement. The anemia which originally was of the hyperchromic

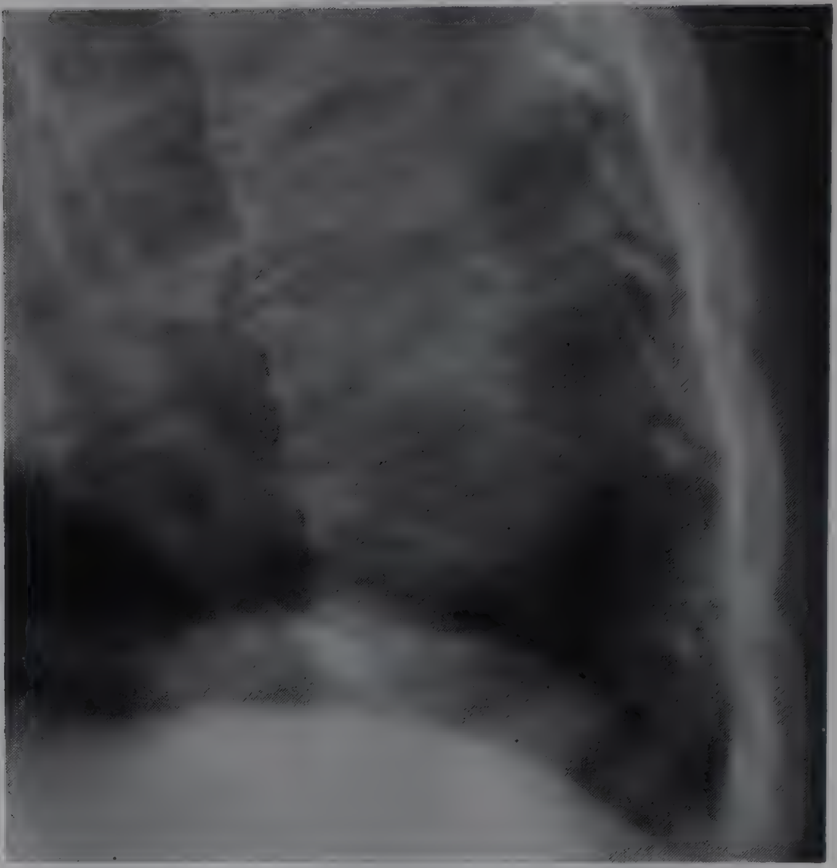


FIG. 11. Case 3, compression of bodies of dorsal vertebrae, Osteomalacia (outlines of bodies touched up).

type was now hypochromic. Roentgenologic skeletal survey revealed persistence of marked generalized demineralization, including the bioconcave appearance of the vertebra and the previously noted healed fractures. Although there was no worsening of the demineralization and no new fractures, there was no distinct improvement in the status of his skeletal system.

Comment: The patient was a 43-year old male with long standing sprue who developed osteomalacia and a number of fractures at different times in different regions. Injections of ACTH resulted in improvement. Persistent anemia and posterior column disease over-shadowed his bone problem.

Case 4

W. S., a 63-year old, white male, presented himself with a complaint of pain in the right lower extremity of six months duration. For 20 years he suffered from a gastric ulcer. Two years prior to his present complaint, he underwent a successful gastric resection. The pain in his right hip was slow in onset and radiated distally into the lower extremity. He had been treated by other physicians for lumbrosacral strain and sciatica without improvement.

On examination there was definite pain and limitation of motion in the right hip. Internal rotation and abduction were limited and painful. The circumference of the right thigh measured one inch less than the left. Neurologic examination was negative. A roentgenogram of the hip revealed osteomalacia and a definite fissure fracture of the neck of the right femur without displacement (Fig. 13). Internal fixation with a Smith-Petersen nail was performed at a private hospital with prompt relief of his pain (Fig. 14). Weight bearing was permitted in five days. His post-operative course was uneventful. Unfortunately, he was not studied as a malabsorption problem but it was considered that he was a case of osteomalacia secondary to post-gastrectomy sprue.

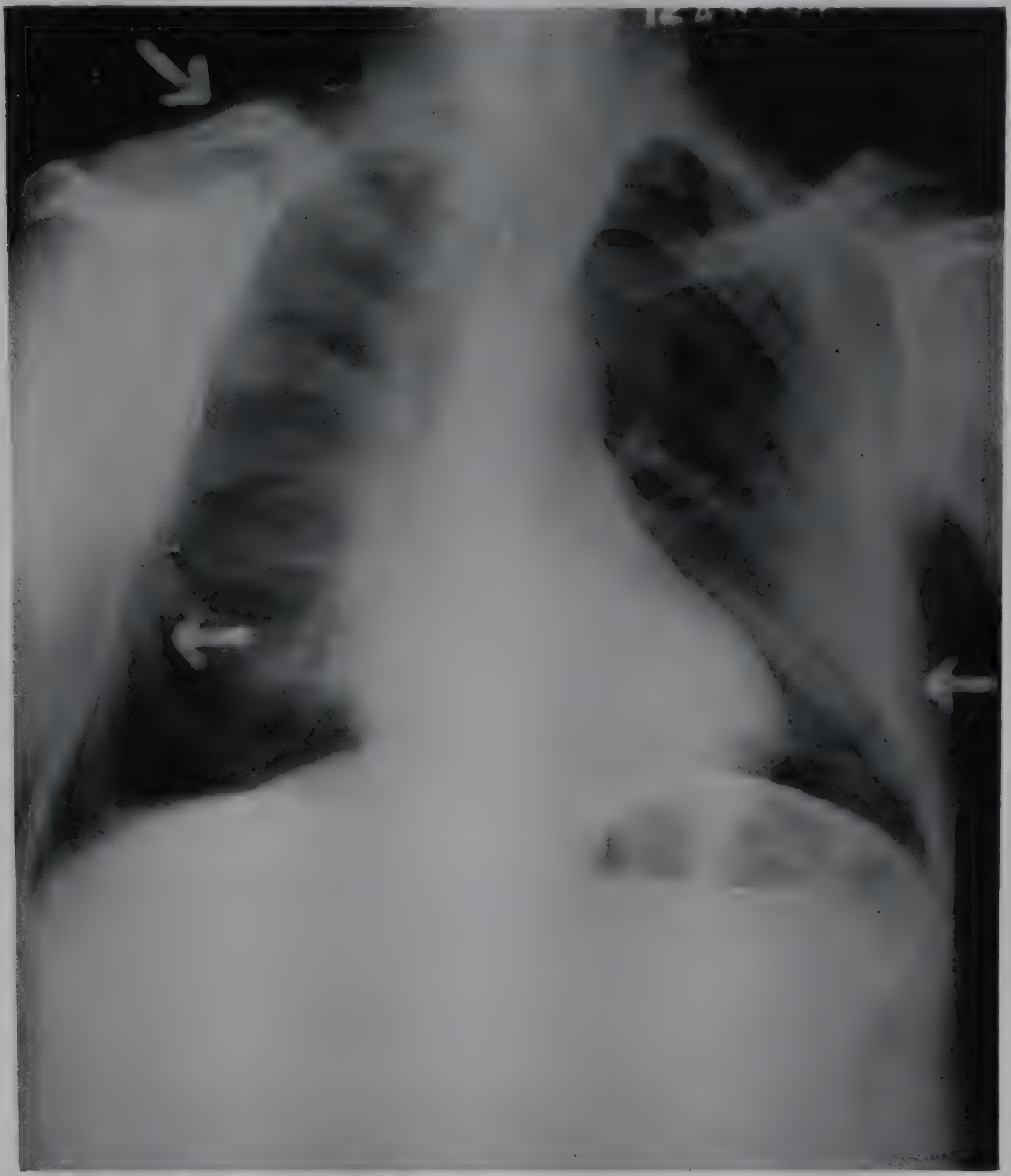


FIG. 12. Case 3, indenting of lower ribs and healed fracture of right clavicle.

Comment: Two years after gastrectomy for long standing ulcer, this patient suffered a fracture of the neck of the femur associated with osteomalacia, probably secondary to malabsorption steatorrhoea. Internal fixation was performed with excellent result.

MECHANISM OF THE DEVELOPMENT OF BONE CHANGES IN MALABSORPTION SYNDROME

The metabolism of the osseous structures of adults is highly dynamic and continuously undergoing steady concomitant break-down and build-up of bone. Organic bone matrix (osteoid) is the basic framework. Mineralization of this lattice work completes the formation of bone.

In sprue and other malabsorption syndromes the intestine fails to absorb fats properly. This results in failure to absorb fat-soluble vitamins, especially vitamin D, which in turn prevents absorption of calcium (15). In addition to the malab-

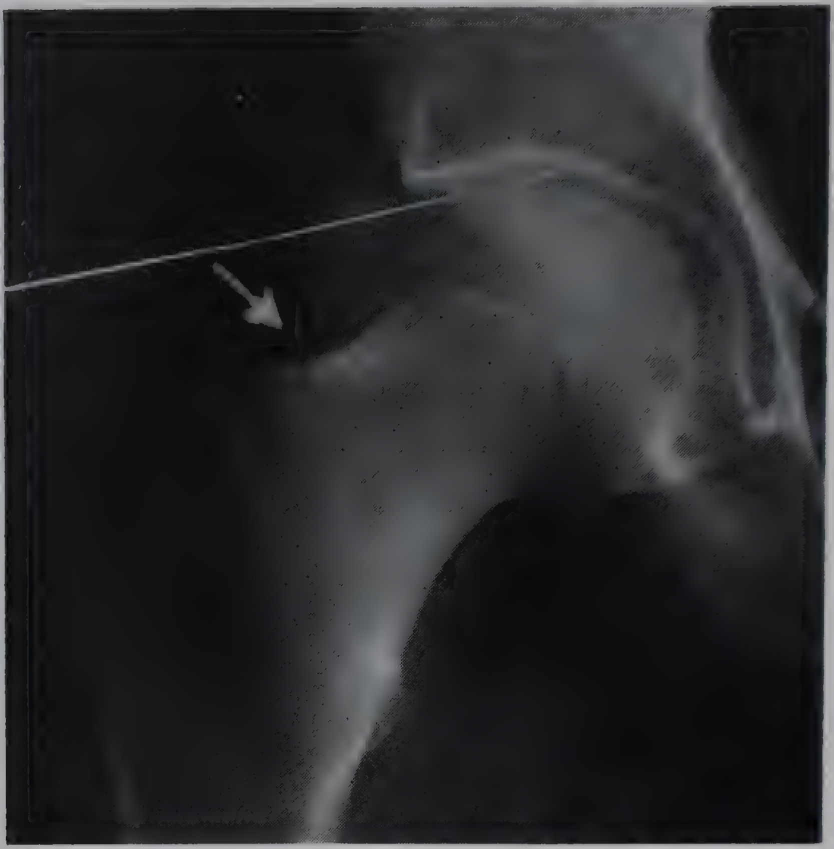


FIG. 13. Case 4, 18 months after subtotal gastrectomy for ulcer of 20 years duration, osseous discontinuity in neck of femur associated with pain and osteomalacia.

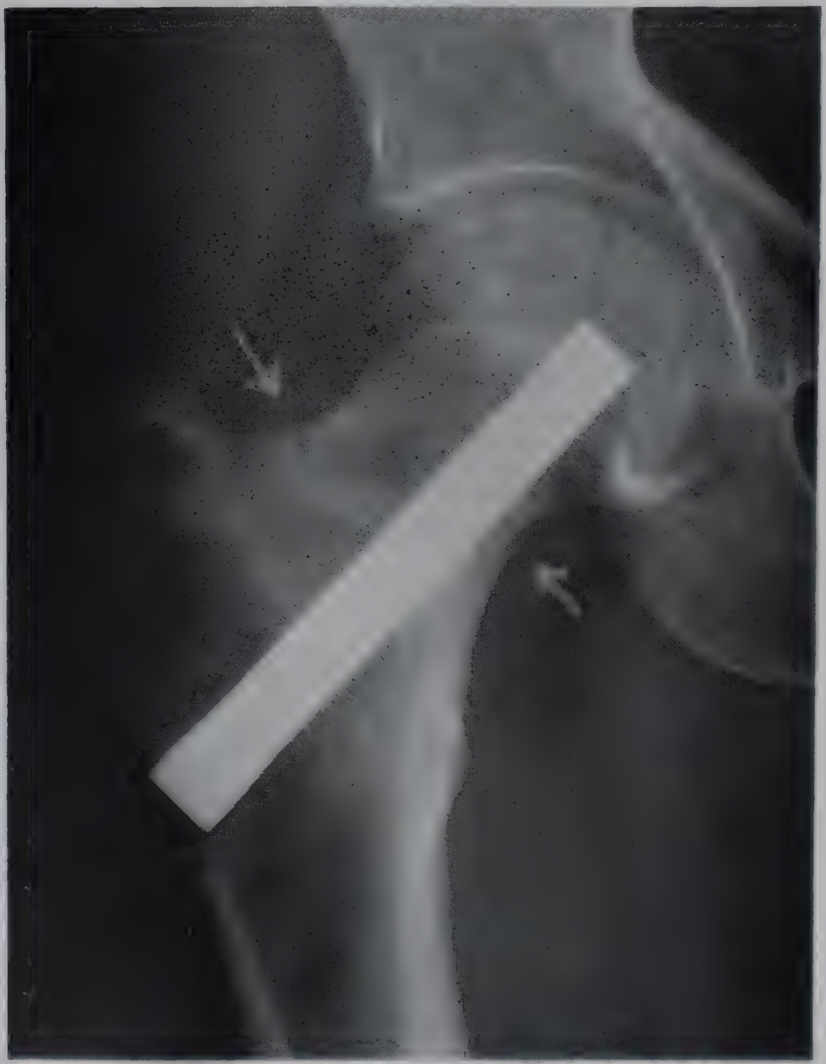


FIG. 14. Case 4, after insertion of Smith-Petersen nail. (Note that post-operatively the osseous discontinuity was more apparent across the entire neck of the femur).

sorption of calcium caused by vitamin D deficiency, considerable amounts of calcium remain unabsorbed because of a combination with the excessive fatty acids in the bowel and the formation of insoluble soaps (17). It is well known that disturbances of pancreatic function as well as disturbances of biliary function impair fat absorption. Ileostomies, extensive resection of the bowel and diffuse intestinal disease may prevent absorption of properly digested fats and vitamins.

Whatever the reason for the deficiency, loss of calcium from the body initiates compensatory mechanisms to restore proper balance (Table I). An increased secretion of parathormone causes breakdown of organic bone matrix, thus releasing bone minerals and restoring blood calcium levels (23). But parathormone also diminishes phosphate reabsorption of the kidney tubules and brings about increased phosphaturia. Loss of phosphate evokes an increase of calcium in the blood from the osseous reservoir (24, 25). A vicious circular process is thus initiated requiring more parathormone to free more calcium to the interstitial tissues and at the same time producing increased excretion of phosphate. As this process continues the osseous structures suffer significant loss of minerals. The feces demonstrate increased fat and calcium content. A diminished urinary calcium excretion develops. When loss of available minerals continues, osteomalacia develops. However, the degree of osteomalacia in sprue bears some

TABLE I.

Schematic presentation of development of osteomalacia

Hypovitaminosis D
↓
Increased fecal calcium due to lack of absorption
↓
Decreased serum calcium
↓
Compensatory parathyroid hyperplasia (or parathyroid adenoma)
↓
Liberation of bone calcium into serum
Loss of urinary phosphorus due to inhibition of tubular reabsorption of phosphorus
↓
Decreased serum phosphorus.

TABLE II

Chart showing highest and lowest values of serum calcium, phosphorus and alkaline phosphatase

CASE	AGE	SERUM		
		Calcium mg./100 ml.	Inorganic Phosphorus mg./100 ml.	Alkaline Phosphatase, King-Armstrong units
1	57	Lowest 7.8	Lowest 1.3	Highest 11
		Highest 10.1	Highest 4.0	Lowest 10
2	62	Lowest 9.4	Lowest 2.8	Highest 22.0
		Highest 10.4	Highest 3.7	Lowest 8.8
3	43	Lowest 5.9	Lowest 2.7	Highest 8.6
		Highest 8.6	Highest 4.5	Lowest 4.6

relation to the degree of exposure to sunshine (26). Excellent observers in the tropics have not seen osteomalacia complicating sprue. The more exposure to sunshine the less the osteomalacia.

A large amount of mineral loss, perhaps as much as 50 per cent, must develop before roentgenographic changes become apparent. This accounts for instances where the blood changes of osteomalacia are present, but the roentgenograms do not reveal demineralization. Fissures in the cortices of the long bones appear. These represent uncalcified osteoid tissue (16, 27). They are variously described as pseudo-fractures, Looser zones or "Umbauzonen" (2). Multiple spontaneous symmetrical pseudo-fractures are referred to as Milkman's syndrome and are manifestations of the same underlying process (3). It has been suggested that the narrow bands of diminished density, which often appear symmetrically and last for months to years in the skeletons of patients with osteomalacia, correspond to the location of main blood vessels which lie on the bones. The mechanical stress caused by the vessels could cause small breaks in the cortex with subsequent laying down of callous, which, in osteomalacia, is uncalcified. This proposed mechanism could explain the symmetrical appearance of the pseudo-fractures in otherwise normal appearing bones and their location at sites not usually subjected to other mechanical stresses (21). If the bone is weakened sufficiently, fractures may result from minor trauma. True pathologic fractures without external trauma may also develop.

In patients with post-gastrectomy sprue the exact mechanism of the defect of absorption has not been studied. It is likely that the existing steatorrhoea is an important factor.

The Role of the Parathyroids

The response of the parathyroid glands to the lowering of serum calcium in sprue may be one of compensatory increase of activity or one of what might be termed parathyroid insufficiency. When hyperparathyroidism occurs in response to the lowered serum calcium, the stimulus to osseous release of calcium deposits aids in maintaining adequate levels of serum calcium. At the same time serum phosphorus is lowered, owing to loss of urinary phosphates. The serum calcium and phosphorus levels are both low. In a long-standing case of sprue in a 41-year old female recently reported, it was noted that the serum calcium was above normal and serum phosphorus low (28). Roentgenograms revealed that a previously noted osteomalacia had progressed into an osteitis fibrosa generalisata. She improved after two parathyroid adenomas were removed. The authors concluded that as a result of her lifelong steatorrhoea she probably passed through a phase of parathyroid hyperplasia before the two adenomas developed. Thus, they concluded, although compensatory hyperparathyroidism is usually reversible following administration of vitamin D, in some cases of long standing steatorrhoea this will not obtain. One or more parathyroid adenomas may develop which will require surgical removal. Despite these findings, one may still raise the question of why some sprue cases develop osteomalacia and some do not? According to some authors (6) it appears to depend on the degree of secondary hyperparathyroidism. If parathyroid insufficiency is present calcium is not mobilized from the bones, serum calcium remains low and tetany may develop. It therefore appears from present evidence that the response of the parathyroid in sprue with either increased function or insufficiency is a secondary factor and not primary. In the absence of techniques for the quantitative determination of circulating parathormone in the blood, the exact role of the parathyroids remains unclear.

DISCUSSION

The proper evaluation of symptoms in idiopathic sprue may require some analysis. Aside from the diarrhea, which may or may not be present, the development of anemia, posterior column and peripheral nerve involvement, and bone softening may cause intermingling and overlapping symptoms. In occult, latent or incomplete sprue, diarrhea is not a prominent feature. Obscure cases of osteomalacia could thus be properly explained (17). The clinician may encounter paresthesias, irritability, tetany and regional pains. In analyzing the cause of pain the clinical picture may suggest arthritis, neuritis, fibrositis or herniation of the nucleus pulposus. Neurologic involvement may appear to be the obvious cause when underlying bone changes are the real instigator of muscular atrophy and weakness. Bone pain may be associated with a developing osteomalacia even in the absence of pseudo-fractures (3). Progressive softening of the bone resulting from osteomalacia may be aggravated by a superimposed osteoporosis—post-menopausal, senile or secondary to corticosteroid therapy. The weakened skeletal structure may become susceptible to lesser degrees of external trauma or even unable to withstand the mechanical requirements of ordinary living. In either situation an interruption or collapse of osseous structure may develop. One of our patients (case 1) was admitted to the neurological service for a sciatic syndrome with atrophy of the left thigh. On x-ray examination of the bones, a fissure fracture of the neck of the femur was discovered as the true cause of his pain. Following internal fixation he improved rapidly, was free of pain and able to ambulate well within a few days.

Differential diagnosis between osteomalacia and osteoporosis is possible in many instances. Roentgenograms in osteomalacia disclose a generalized demineralization, whereas in osteoporosis it is manifested mostly in the spine and pelvis. Serum calcium, phosphorus and alkaline phosphatase are normal in osteoporosis but are altered in osteomalacia. The Sulkowich test is positive in osteoporosis and negative in osteomalacia. Despite the differential features listed above many patients will present intermingling of osteomalacia and osteoporosis and simultaneous treatment of both conditions is indicated.

ORTHOPEDIC MANAGEMENT

The treatment of fractures in sprue or malabsorption in addition to general therapy consists of reduction and/or fixation. Internal fixation for fractures of the neck of the femur, and the use of braces and early ambulation for compression fractures of the spine are employed. Present day trends in orthopedics have drifted away from the older idea of attempting hyperextension reduction of compression fractures of the spine and the application of a full body cast. Instead, a brief period of rest sufficient to alleviate the pain is favored, followed as soon as possible by gradual increasing ambulation with the support of a back brace (29).

Decreased physical activity tends to increase deossification. Correction of the underlying malabsorption is essential. However, as illustrated in some of our cases, failure to respond to the treatment of sprue may necessitate the use of corticosteroids. Since this form of therapy, although beneficial to idiopathic steatorrhoea, will aggravate the bone softening and add osteoporosis to the osteomalacia, corticosteroids must be held in reserve and employed only when all other methods have proved inadequate. It is claimed that prednisone and prednisolone have less of a deossifying effect than other corticosteroids but further observations are necessary before this is confirmed in cases of malabsorption syndrome. The smallest effective dose should be used and osteoporosis must be counteracted by high mineral and high protein intake. Vitamin D should be employed, preferably parenterally. Ultraviolet radiation to the skin would also be helpful. In some instances as much as 300,000 units of vitamin D should be administered daily (8). Testosterone should be used in suitable doses.

CONCLUSIONS

1. Observations on the occurrence of osteomalacia, usually associated with osteoporosis, in the malabsorption syndrome are reported.
2. Three cases in which idiopathic sprue was the underlying cause of the osteomalacia and one case in which bone changes followed a subtotal gastrectomy (post-gastrectomy sprue) are presented.
3. The mechanism of development of osteomalacia and osteoporosis is reviewed and the role of the parathyroid is discussed.
4. Corticosteroids, although helpful in the control of idiopathic steatorrhoea, enhance osteoporosis and further embarrass osseous integrity.
5. Management of the underlying osteomalacia and osteoporosis and treatment of the fractures is discussed.
6. Incomplete sprue may cause osteomalacia despite the absence of overt intestinal symptoms.

ACKNOWLEDGEMENT

The author wishes to thank Dr. David Adlersberg for his inspiration and guidance of this study and his permission to publish cases one, two and three. He and his staff in the Nutrition Laboratory have followed these patients for many years.

REFERENCES

1. Holst, J. E.: Ein in Danemark aufgetretener Fall Von Sprue. Acta. Med. Scand., 66: 74, 1927.
2. Looser, E.: Uber Spatrachitis und Osteomalacis Kliniche, rontgenologische und Pathologisch Anatomische Untersuchungen. Chi., 152: 210, 1920.
3. Milkman, L. A.: Pseudofractures (Hunger Osteopathy, Late Rickets, Osteomalacia). Am. J. Roent., 24: 29, 1930.

4. Anderson, A.: Milkman Syndrome in Idiopathic Steatorrhoea Complicated by Refractory Macrocytic Anemia. Lancet, 2: 897, 1950.
5. Adlersberg, D.: Problem of Management of Idiopathic Sprue. N. Y. State J. Med., 55: 3575, 1955.
6. Salvesen, H. A., and Boe, J.: Osteomalacia in Sprue. Acta. Med. Scandinav., 146: 290, 1953.
7. Badenoch, J., and Fourman, P.: Osteomalacia in Steatorrhoea. Quart. J. Med., 23: 165, 1954.
8. Langmead, F.: Idiopathic Steatorrhoea with Early Osteomalacia. Proc. Roy. Soc. Med., 28: 1643, 1935.
9. Short, D. W.: Osteomalacia Associated with Steatorrhoea: Report of a Case. Glasgow, M. J., 29: 53, 1948.
10. Pilcher, M. F.: Osteomalacia Due to Steatorrhoea: Report of a Case. Postgrad. Med. J., 30: 601, 1954.
11. Bennett, T. I., Hunter, D., and Vaughan, J. M.: Idiopathic Steatorrhoea (Gee's Disease): A Nutritional Disturbance Associated with Tetany, Osteomalacia and Anemia. Quart. J. Med., 1: 603, 1932.
12. Adlersberg, D., and Schein, J.: Clinical and Pathological Studies in Sprue. J.A.M.A. 134: 1459, 1947.
13. Hanes, F. M.: Sprue. Tice's Practice of Medicine. Vol. IV.
14. Paterson, M. R. C. P.: The Sprue Syndrome. Am. J. Med. Sci., 231: 92, 1956.
15. Bauer, W., and Marble, A.: Studies of the Mode of Action of Irradiated Ergosterol II. Its Effects on Calcium and Phosphorus Metabolism of Individuals with Calcium Deficiency Diseases. J. Clin. Invest., 11: 21, 1932.
16. Strang, C.: The Looser-Milkman Syndrome—Occurrence in a Case of Idiopathic Steatorrhoea. Brit. J. Surg., 38: 489, 1951.
17. Juergens, J. L., Scholz, D. A., and Wollaeger, E. E.: Severe Osteomalacia Associated with Occult Steatorrhoea Due to Nontropical Sprue. A.M.A. Archiv. Int. Med., 98: 774, 1956.
18. Albright, F., and Reiferstein, F. C.: The Parathyroid Glands and Metabolic Bone Disease. The Williams & Wilkins Co., Baltimore, 1948.
19. Snapper, I.: Medical Clinics on Bone Diseases. 2nd Ed. 1949. Interscience Publishers Inc.
20. Snapper, I., Seely, R., Flak, S., and Feder, E.: Osteomalacia in New York. Ann. Int. Med., 41: 893, 1954.
21. LeMay, M., and Blunt, J. W.: A Factor Determining the Location of Pseudo-Fractures in Osteomalacia. J. Clin. Invest., 28: 521, 1949.
23. Carnes, W. H.: The Demonstration of an Effect of Parathyroid Extract on Bone Matrix. Am. J. Path., 736: 26, 1950.
24. Telfer, S. V.: Studies on Calcium and Phosphorus Metabolism. I. The Excretion of Calcium and Phosphorus. Quart. J. Med., 16: 45, 1922.
25. Snapper, I.: Parathyroid Hormone and Minerals Metabolism. Bull. N. Y. Acad. Med., 29: 612, 1953.
26. Suarez, R. M.: Clinical Review of Sprue Based on the Study of 150 Cases. Puerto Rico J. Pub. Health, 14: 157, 1938.
27. Seeliger, D.: Spaltbildungen in den Knochen und Schleichende Frakturen bei den sogenannten Hungerknochenerkrankungen. Arch. F. Klin. Chir., 122: 588, 1923.
28. Davies, D. R., Dent, C. E., and Wilcox, A.: Hyperparathyroidism and Steatorrhoea. Brit. Med. J., 2: 1133, 1956.
29. Bick, E.: Management of Fractures of the Vertebrae in the Aged. Am. J. Surg., 87: 5764, 1954.

THE ROENTGEN FINDINGS IN THE MALABSORPTION SYNDROME

RICHARD H. MARSHAK, M.D.,

BERNARD S. WOLF, M.D.,

New York, N. Y.

AND

JOAN ELIASOPH, M.D.

Stamford, Conn.

It has been known for many years that disorders of absorption from the gastrointestinal tract may be reflected in abnormalities of the radiographic pattern of the small intestine. The essential features of this pattern are dilatation, segmentation, hypersecretion, changes in motility and mucosal markings. These changes have been considered non-specific since they occur in a variety of conditions, some associated with diseases of malabsorption, such as sprue, Whipple's disease, and lymphosarcoma, but also in many other conditions having no relation to malabsorption, such as hookworm disease, hyperthyroidism, allergy and emotional disturbences. Numerous terms have been used loosely to bind the roentgen findings in these heterogeneous conditions, i.e. deficiency pattern, disordered motor function, segmentation or irritation patterns and enteropathy in deficiency states (1). Minimal degrees of dilatation, segmentation and hypersecretion may occur in many unrelated diseases. When the changes are marked and occur in particular combinations, however, they are usually found only in association with certain malabsorptive states, namely, sprue, lymphosarcoma and Whipple's disease. The roentgen findings, therefore, are more specific than hitherto suspected and sufficiently characteristic to be of diagnostic value.

The term malabsorption syndrome has recently been applied to diseases which are characterized by alterations in absorption of nutrients from the intestinal tract. Fats, because of their insolubility in aqueous solutions, are relatively difficult to absorb. It follows, therefore, that difficulties which patients have with intestinal absorption, are often characterized by excessive amounts of fat in the stool, i.e. steatorrhea.

The causes of symptomatic steatorrhea can be classified into three main groupings:

1. Idiopathic steatorrhea
2. Pancreatogenous steatorrhea
3. Secondary steatorrhea (organic lesions of the gastrointestinal tract).

Since these three groups represent the majority of the cases with symptomatic steatorrhea, the roentgen findings encountered in these cases will be described.

HISTORY

The first recorded roentgen studies of the intestinal tract in patients with sprue were reported by Pillai and Murthi in 1931. They studied nine cases of

---

From the Department of Radiology, The Mount Sinai Hospital, New York, N. Y.

sprue in India and noted changes in motility and tone of the stomach and colon. The small intestine emptied rapidly and in one case "a part of the terminal coil of the ileum was dilated. The cecum showed dilatation . . ." (2). In 1932, Bennett, Hunter and Vaughan, reporting 16 cases of idiopathic steatorrhea, noted the roentgen changes in the intestinal tract were largely confined to the colon, which manifested slight to extreme dilatation. They commented that the abdominal distention which is such a conspicuous feature of this disease also could be due to the small intestine (3). Mackie, in 1933, reported a case of non-tropical sprue which showed dilated coils of jejunum suggesting a lack of tone. Hypermotility was also noted (4). Snell and Camp, in 1934, in a report of seven cases of chronic idiopathic steatorrhea, were the first to report in detail the roentgen alterations in the small intestine. They observed delayed motility, changes in mucosal relief occasioned by smoothing of the bowel contours, and obliteration of the valvular markings. The barium was observed to clump in elongated masses. They stated that these findings were not characteristic of this disorder, but "may occur in varying degrees in any diffuse inflammatory condition of the intestinal tract" (5). Mackie, Miller and Rhoads (1935) reported on the roentgen changes in the small intestine in 17 cases of sprue. These authors appear to be the first to have utilized the term "segmentation" to describe the segmental distribution of barium within the small intestinal loops. In addition to the findings previously reported by Snell and Camp, they noted dilatation of the bowel lumen (6). Following these reports, similar small intestinal changes were noted in many varied conditions, chronic ulcerative colitis (7), chronic idiopathic adult tetany (8), celiac disease (1), pancreatic insufficiency (9), icterus (10), lymphosarcoma (11), allergy (12, 13), Whipple's disease (14) and tuberculosis (15).

To the growing roentgen literature on sprue, Kantor (1939) contributed the term "moulage" to describe the appearance of the bowel in this condition which "resembles a tube into which wax has been poured and allowed to harden" (16).

In 1941, Golden, correlating previous reports with observations on his own cases, noted the similarity in the roentgen appearance of the small bowel in a multitude of clinical entities as well as that seen in normal newborns. He postulated a common mechanism operating in the production of these similar phenomena from so many causes, i.e. damage to the intramural nervous system of the small intestine. To describe these roentgen findings, he introduced the term "deficiency pattern" because so many of his early cases were actually deficiency states (17, 1). It soon became apparent that the cases were not necessarily associated with deficiency diseases and the terms "disordered motor function" or "irritation pattern" were preferred. Despite the confusing nomenclature, these terms served to focus attention upon these little-known and elusive small intestinal disorders.

Sussman and Wachtell (1942, 1943) did not concur in the hypothesis that there was a common neurogenic mechanism operating in producing this pattern. By giving atropine to tolerance to normal subjects, the "deficiency pattern" could not be produced. They concluded, therefore, that degeneration of the intramural nerve plexuses was not a factor. Based on the postulate that the pattern in sprue might be caused by overactivity of the parasympathetic nervous system, large doses of atropine were given to sprue patients without significantly altering the roentgen findings. Concluding that the findings of the "deficiency pattern" are not necessarily variations of a single pattern with a common neurogenic cause, they stated that submucosal changes, muscle or nerve damage, modified by abnormal bowel content or unusual hormonal or nervous stimuli, could individually or in combination produce this pattern (18, 19).

Utilizing balloon techniques in two patients with sprue, Ingelfinger and Moss (1943) demonstrated that the small intestine in sprue lacks tone, possibly accounting for the ineffectiveness in advancing intestinal contents and thus producing segmentation. Furthermore, they observed that intestinal contractions responded to Mecholyl and not to Prostigmin and suggested that the nervous apparatus of the small intestine in sprue fails to liberate active acetylcholine (20).

Attempts have been made to reproduce in normal subjects the small bowel pattern in sprue. In 1936, Pendergrass, Ravdin, Johnston and Hodes studied the effects of various foodstuffs on the small intestinal pattern. With an olive oil-barium-water preparation they were able to produce a picture similar to that seen in some cases of sprue, with minimal segmentation, hypomotility and some dilatation of the bowel lumen (21). In 1949, Frazer, French and Thompson were able to induce segmentation and produce a picture which they considered to be radiologically indistinguishable from the "deficiency pattern" by the introduction of fatty acids, hypertonic solution or mucus into the small intestine of a normal individual. They produced flocculation of barium in vitro when added to mucus-containing secretions and attributed the segmentation pattern in sprue to increased mucus content of the bowel produced by the irritation of fatty acids. It was suggested by these investigators that, unless the possibility of flocculation of barium has been excluded, the segmentation pattern cannot be regarded as evidence of vitamin deficiency or disordered motor function (22). Ardran, French and Mucklow (1950), utilizing a non-flocculating barium suspension in patients who had previously shown a segmentation pattern with routine barium preparations, were able to prevent segmentation and maintained the contrast agent in a continuous column, noting only dilatation (23). It has become apparent, therefore, that the segmented clumps of barium do not reflect the morbid anatomy of the surrounding intestine because they do not outline the bowel wall and interpretation of mucosal alterations or narrowing of the lumen under these circumstances may be misleading.

In 1954, Adlersberg et al. and Marshak, Wolf and Adlersberg, describing the clinical and roentgen alterations they observed in 40 patients with idiopathic sprue, presented the concept of the sprue pattern. This pattern consisted primarily of dilatation of the small intestinal loops, hypersecretion and segmentation. They considered that when this pattern was observed with sufficient intensity, the diagnosis of sprue could be suggested radiologically (24, 26).

TECHNIQUE OF ROENTGEN STUDY

The small intestine was studied following the administration of a mixture containing 10 ounces of barium sulfate by volume to which had been added enough water to make 20 fluid ounces. The ordinary commercial USP barium sulfate preparation was used. The initial film was made at 15 minutes and another after a 15 minute interval. Further filming depended on the rate of passage of the barium meal and usually consisted of an examination every 30 to 60 minutes until the barium left the small intestine. It was occasionally necessary when large segments of small intestine pooled the barium to administer an additional four or six ounces of the mixture to secure adequate visualization of the small intestine. Neither saline nor icewater were administered because these preparations in themselves, in our experience, disturbed the small intestinal pattern.

In the interpretation of diffuse lesions of the small intestine, large quantities of barium should be used so that many intestinal loops may be visualized in continuity at the same time. In sprue, for example, the loops of bowel may be so dilated that small amounts of barium administered may pool in a single segment. Small amounts of barium may not reflect the morbid anatomy of the small intestine due to incomplete filling and frequently the incomplete distention may simulate an abnormality.

Ardran, French and Mucklow have stated that with the use of their micropulverized barium preparation, segmentation which is so frequently seen in malabsorptive states can be prevented and a continuous barium column produced (23). This is advantageous in recognizing the organic structure of the small intestine. It may have the disadvantage, however, if used on the initial examination, of obscuring the functional changes which may aid in the diagnosis of malabsorptive states.

THE ROENTGEN FINDINGS IN IDIOPATHIC STEATORRHEA OR SPRUE

Forty-six patients with sprue were studied. Some of these findings have been previously reported (24, 26). In six patients, a normal small intestinal pattern was found. The remaining 40 patients exhibited in varying degrees the small intestinal changes that have been described by many authors, namely, dilatation, segmentation, fragmentation and scattering of the barium column, thickening of the mucosal folds, hypersecretion, fluid levels, the "moulage sign" and motility changes (24, 25, 17, 1, 26).

Dilatation. Dilatation of the lumen of the small intestine is one of the most important and constant findings in sprue. Some of the individual features of the sprue pattern are seen in other disorders, but in none is dilatation more striking or constant than that associated with sprue.

Dilatation is the most frequent of the roentgen findings in sprue and was found in 40 of 46 cases. It is usually best visualized in mid- and distal jejunum (Figs. 1A and 1B). Dilatation of the distal ileum is not as common as elsewhere in the small intestine. In three cases, the entire small intestine was dilated. The dilated loops are generally long and tortuous in course with pliable walls. The *valvulae conniventes* are prominent (Figs. 2A and 2B). The degree of dilatation is exceedingly variable and often a single intestinal segment may manifest varying degrees of dilatation during the course of a single roentgen study. In four cases, dilatation was marked (Fig. 3A). In 16 cases, the lumen of the dilated intestinal loops was three times the normal caliber; in 16 patients the dilatation was twice normal and in four patients, it was mild. In general, however, dilatation appears to be related to the severity of the disease and was most marked in the advanced cases. The large intestine may also show dilatation which can be pronounced.

Fluoroscopic observations of the altered contractility of the dilated small intestinal loops are of some interest. In many patients, the barium column flowed more freely than usual through the dilated intestinal loops, apparently

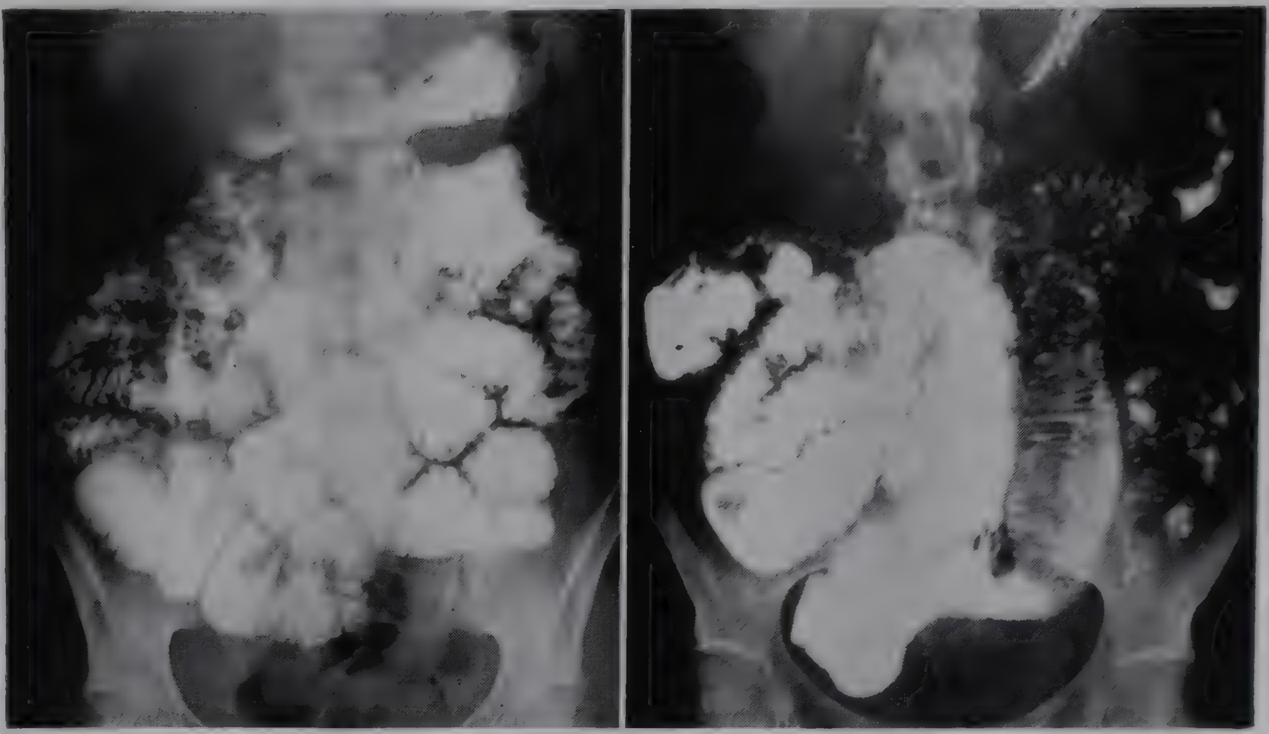


Fig. A Fig. B

Fig. 1A. Moderate dilatation of mid- and distal jejunum.

Fig. 1B. Moderate dilatation of mid- and distal jejunum. Note the "functional intussusception" at the end of the barium column.

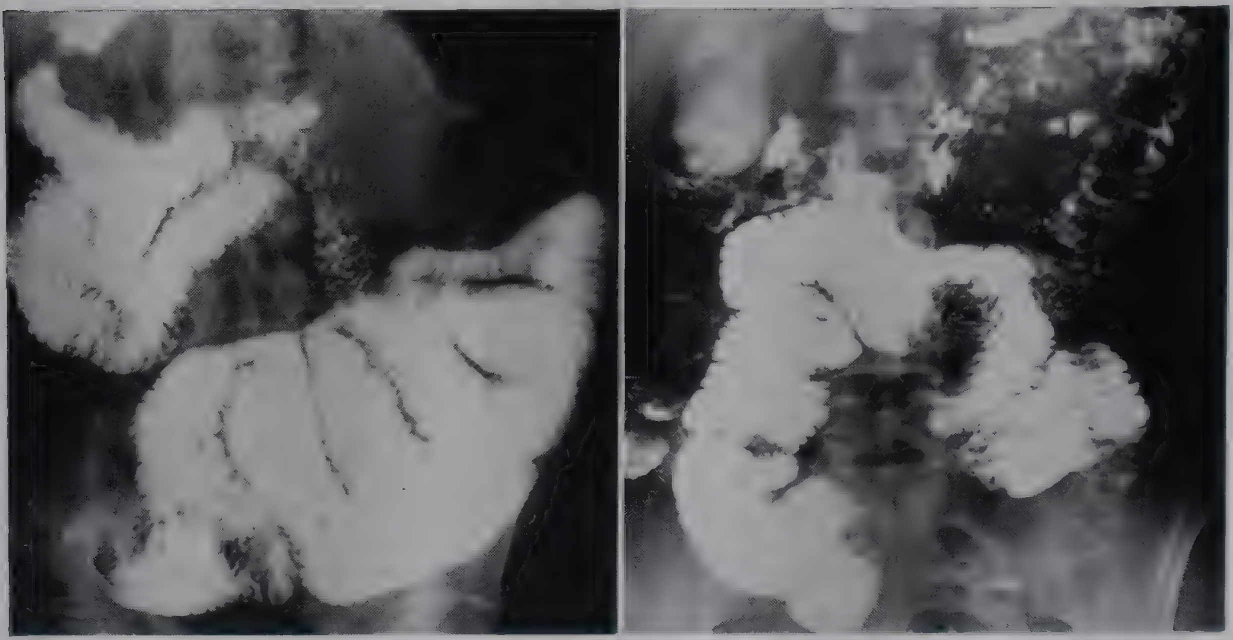


Fig. A Fig. B

Fig. 2A. Moderate diffuse dilatation of the jejunum with prominent valvulae conniventes.

Fig. 2B. Moderate dilatation of the mid-jejunal loops with prominent valvulae conniventes. The loops are pliable.

unhindered by the tone of the contracted segment found normally ahead of the barium column. When secretions were encountered, progress was slowed and the column segmented. Conversely, in some patients with marked dilatation, there was prolonged transit time which appeared to be due to ineffective peristaltic activity. These fluoroscopic findings suggest that the tonicity of the small intestine in sprue is altered, offering little resistance to dilatation by ingested substances, possibly even secretions, and that, once dilated, peristalsis becomes

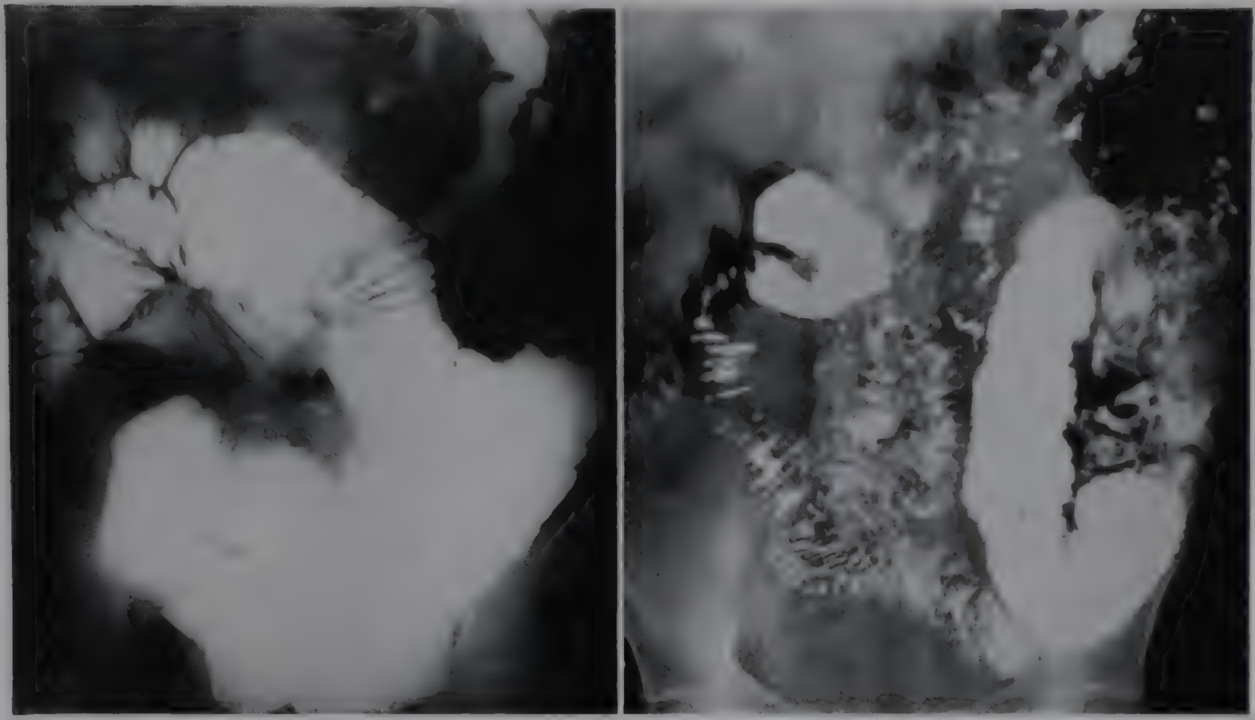


FIG. A FIG. B

FIG. 3A. Marked dilatation of mid- and distal jejunum with prominence of mucosal folds. At autopsy, the mucosa of the small intestine was flat and atrophic.

FIG. 3B. Delayed segmentation. The intestinal loops are dilated. Secretions are increased and there is fragmentation of the barium column.

disordered and ineffective. It has been shown experimentally that, if the intraluminal pressure within an isolated loop of small intestine is increased beyond a certain point, the stretch reflex is no longer in operation and the bowel wall will not contract (27). Decompensation of the bowel wall may occur in severe cases of sprue with marked prolonged small intestinal dilatation.

Secretions, in themselves, do not appear to be a factor in the production of dilatation. Dilatation is generally most marked in the jejunum where secretions are least, and minimal in the ileum, where excessive secretions are most often found.

Patients with prolonged diarrhea due to any cause may develop potassium deficiency. In animals, dilatation of the small intestine has been produced following potassium depletion. It appears that potassium is necessary in the mediation of nerve impulses and the alterations in potassium may produce an autonomic imbalance (1). If this is a factor, why only the small intestine is affected, and not other autonomic functions such as sweating or pilomotor activity, is of considerable interest.

The cause of dilatation remains unknown. At autopsy, the only finding may be thinning of the small intestinal wall. Whether this finding is the cause of the dilatation or its sequela has been subject to speculation.

Segmentation. Segmentation was seen in 32 of 40 patients with abnormal small intestinal patterns. The term segmentation in this study has been restricted to indicate only those masses of barium which are large, definitely separated from adjacent clumps, usually dilated and contain excessive secretions. The small, contracted, barium-filled segments of small intestine connected by strands of barium seen in association with spasm are not included in this definition.

Segmentation was most pronounced in the ileum and was best seen in the more advanced cases. Two forms were noted, immediate and delayed. The more common form was delayed segmentation, i.e. segmentation that occurred in those intestinal segments that were in the process of evacuation (Figs. 3A and 3B). The less common, immediate segmentation was noted as soon as the barium entered the small intestine and persisted throughout the study (Figs. 4A and 4B). In a mild or moderately severe case of sprue, diffuse dilatation of the jejunum and proximal ileum was noted followed by segmentation of the barium column in the distal ileum (delayed) (Figs. 7A and 7B). In the more severe cases, segmentation was immediate (Fig. 4A). The difference between the two forms of segmentation may be accounted for by the amount of secretions within the intestinal tract. In those patients with markedly increased secretions, segmentation appeared to be immediate.

Between the segmented clumps of barium, worm- or string-like strands of barium were often noted. These seemingly collapsed intestinal loops were usually associated with segmentation. They were inconstant and varied from film to film appearing to be due to possibly altered motor activity of the bowel segment or to incomplete filling and emptying (Figs. 5A and 5B). Since these seemingly collapsed segments only occurred in the presence of segmentation (which was always associated with hypersecretion), they may actually represent only the barium stream as it passes through a secretion-filled loop (Figs. 5A and 5B).

As the barium leaves the small intestine, a faint, irregular stippling of residual barium may be seen along the course of the jejunum. This is a normal finding. However in sprue, the mottling is coarser and more amorphous, resembling soap flakes. This is called scattering and is usually associated with segmentation and increased secretion. The term fragmentation has also been used to describe this finding (Figs. 3B and 4B).

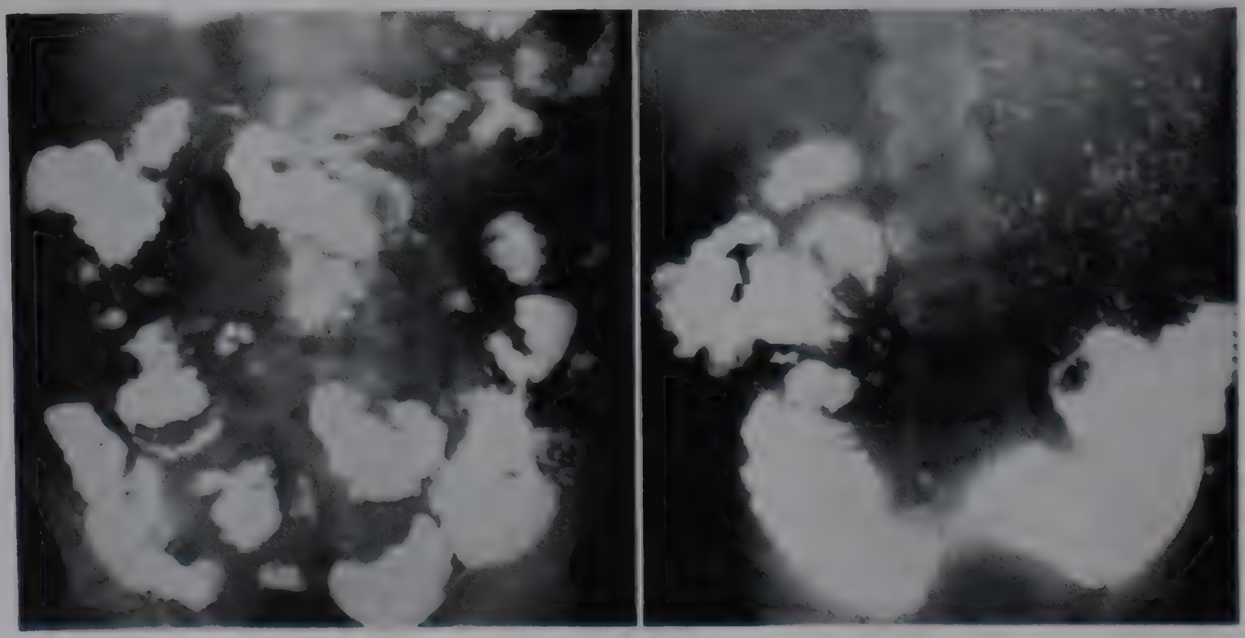


FIG. 4A FIG. 4B

FIG. 4A. Immediate segmentation occurring throughout the small intestine.
FIG. 4B. Immediate segmentation with moderate dilatation. There is fragmentation of the barium column in the jejunum.

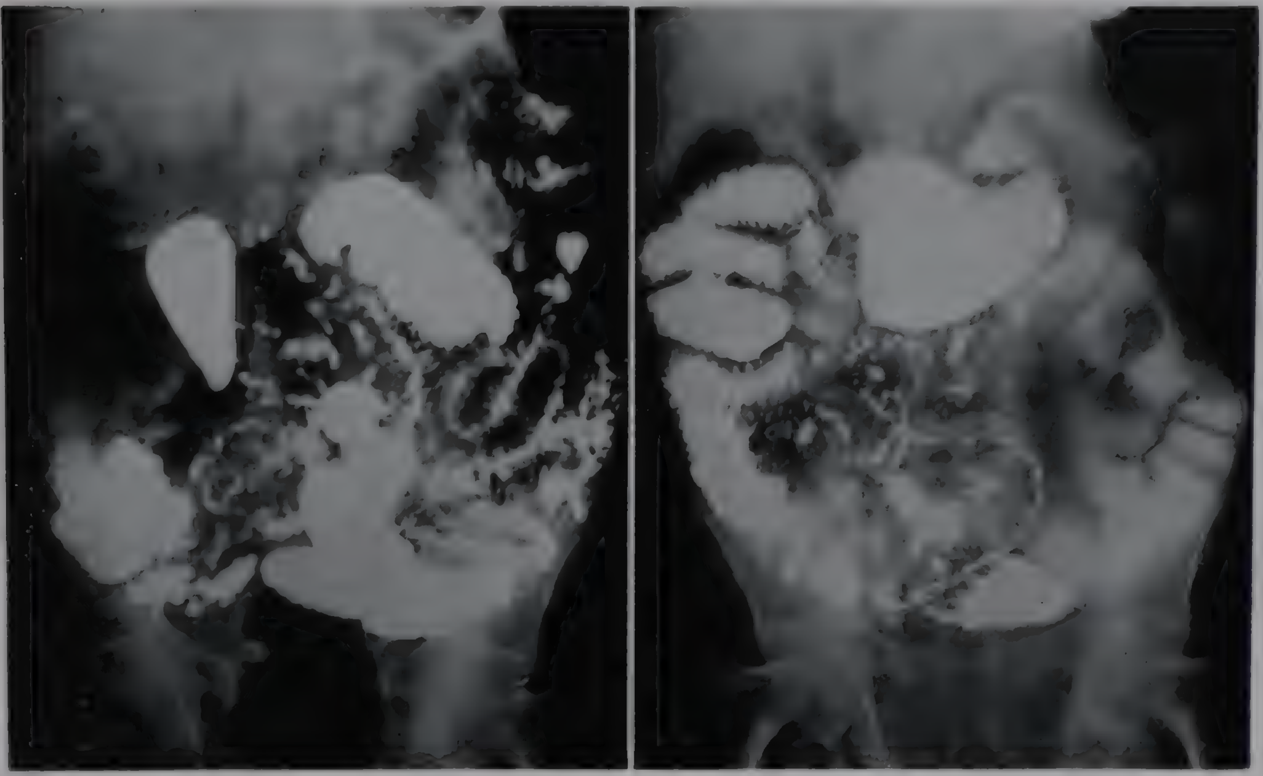


FIG. 5A FIG. 5B

FIG. 5A. Delayed segmentation, increased secretions, worm-like intervening segments possibly caused by abnormal contractions or the barium column passing through a secretion-filled intestinal loop.

FIG. 5B. Same case as 5A, a few minutes later. Note the changing appearance of the dilated and seemingly contracted intestinal loops. The increased fluid content of the bowel is more apparent.

Another form of abnormal distribution of barium seen with hypersecretion is the distorted, slightly thickened, irregular, slightly blunted folds which vary considerably from film to film. These changes can be seen in sprue and also in other instances in which secretions are increased or altered (Fig. 11C).

Hypersecretion. An excessive amount of secretion in the intestinal tract is a constant phenomenon in most cases showing the sprue pattern and especially in those with marked segmentation. Air fluid levels may be seen occasionally during the course of study. The usual homogenous appearance of the barium in the normal small intestine is replaced by barium which presents a coarse granular appearance with areas of flocculation dispersed irregularly in the barium-filled loops. Flocculation is best visualized at the periphery of the segment (Figs. 4A and 4B).

Thickening of the folds. When dilatation of the jejunum occurs, whether due to mechanical or functional changes, the mucosal folds rather than becoming flattened are prominent and seemingly enlarged. In sprue, the *valvulae conniventes* in the dilated jejunum appear remarkably conspicuous (Figs. 2B and 3A). This is in contrast to the usual autopsy findings of a smooth atrophic mucosa. The dynamic state of the bowel is not reflected in the post-mortem findings and it would appear that the prominent mucosal folds produced by an active *muscularis mucosa* are lost.

The thickening of the folds seen in lymphosarcoma and Whipple's disease is more readily understood. The actual infiltration of mucosal and submucosal

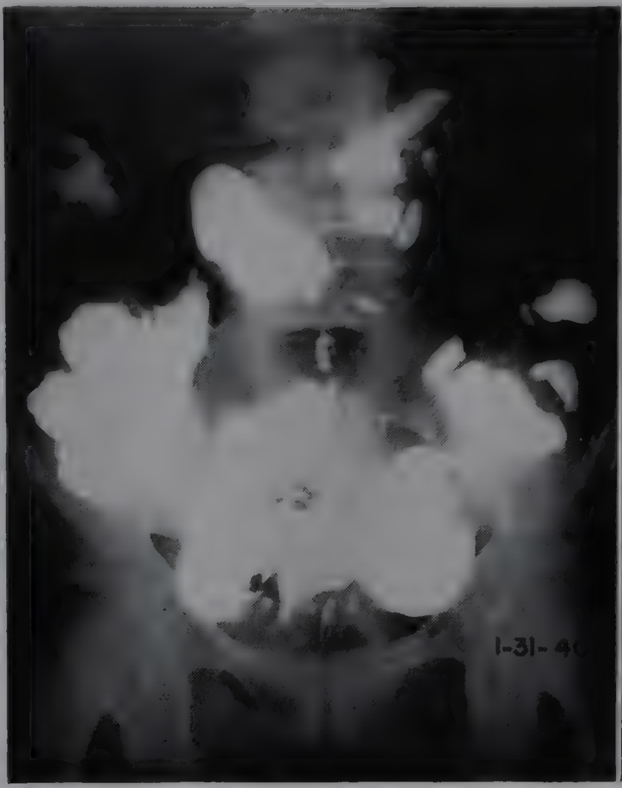


Fig. 6A

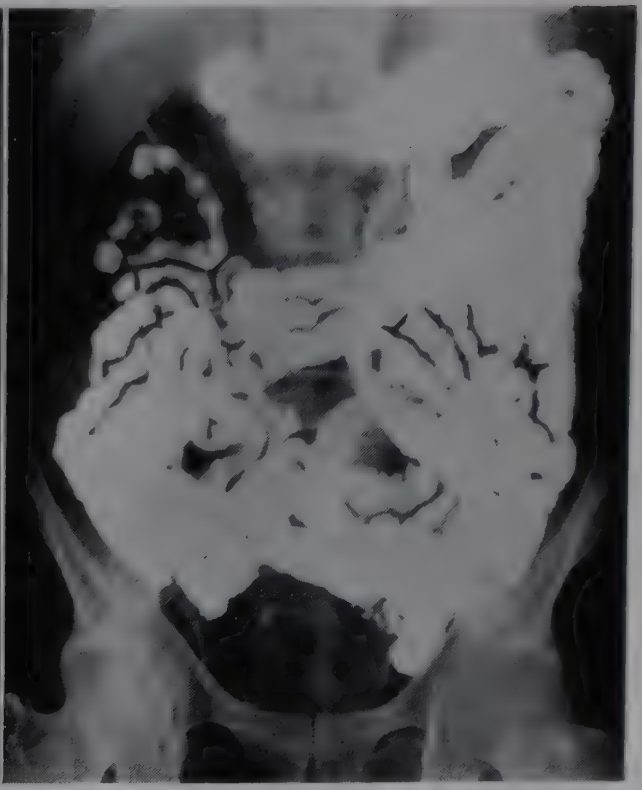


Fig. 6B

Fig. 6A. Immediate and persistent segmentation, increased secretions, moulage sign.
Fig. 6B. Same patient as 6A, six months after the initiation of anti-anemic therapy.

layers of the bowel wall produce thickening, stiffening and rigidity of the infiltrated area with accompanying reactive edema.

Transit time. Transit time refers to the interval during which the barium traverses the small intestine and enters the cecum. The average time in adults has been found to be approximately three hours; however, there is a wide range of normal variation. In most of the patients with sprue, transit time varied from three to five hours. In a few, it was less, diminishing to as little as 30 minutes. In four patients, it was as long as six and seven hours. In none was there marked prolongation of transit time. This may be accounted for by the fact that we have used larger quantities of barium than are usually employed and thereby tend to overcome the effect of puddling of barium in a single dilated segment.

Moulage sign. This term has been utilized to describe the roentgen appearance of the jejunum in sprue in which the folds appear to be completely effaced and the barium-filled lumen resembles a tube into which "wax has been poured and allowed to harden" (Figs. 5A and 6A). It was most frequently noted in association with hypersecretion and segmentation (Fig. 6A). In these cases the secretions probably obscured the mucosal markings. In a few cases, no mucosal markings were seen even when there was no dilatation and no hypersecretion. The bowel wall appeared flaccid. The cause of the moulage sign in these cases is not clear (Fig. 8A).

THE APPEARANCE OF THE SMALL INTESTINE IN SPRUE FOLLOWING THERAPY

The impression of improvement in the small intestinal pattern in patients treated for sprue must be evaluated with care because marked variations in the

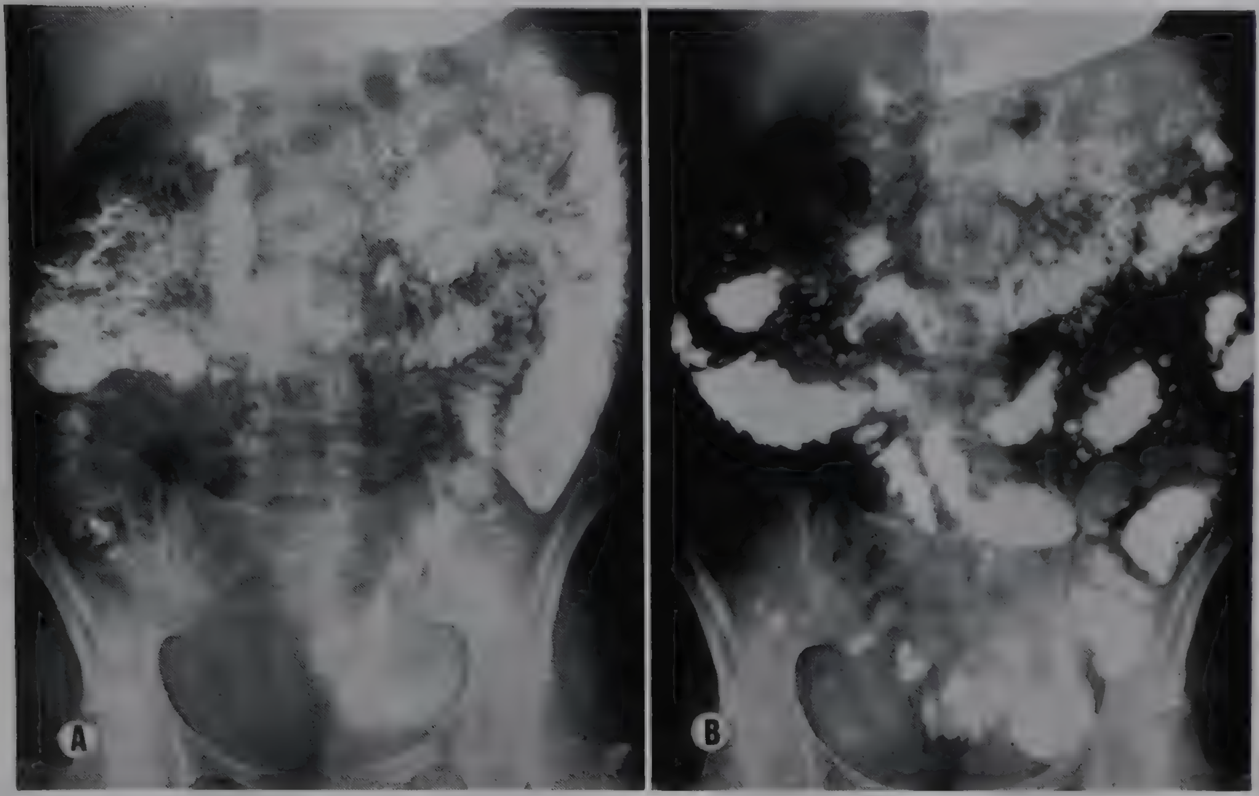


FIG. 7A. Slight dilatation of mid- and distal jejunum.
FIG. 7B. Same patient as 7A, one-half hour later, showing delayed segmentation and increased secretions.

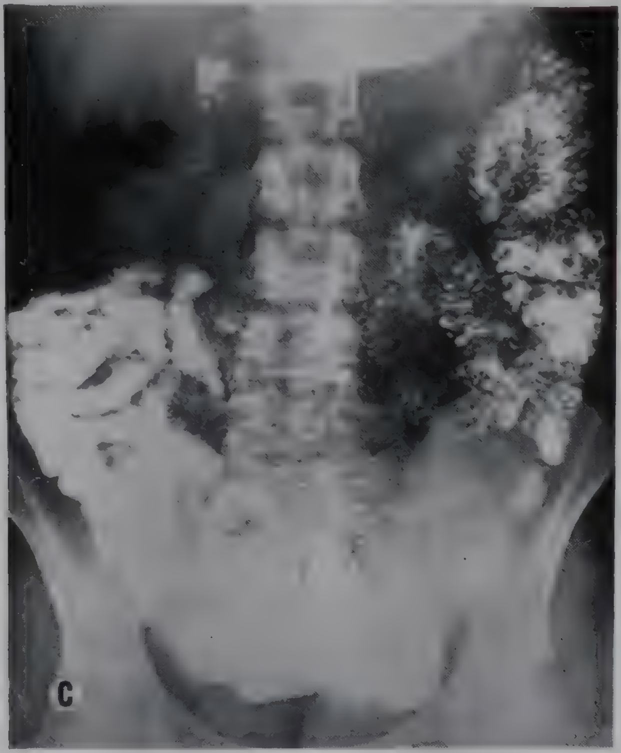


FIG. 7C. Same patient as 7A and 7B. After three months of cortisone therapy, the small intestinal pattern shows only minimal alterations in the appearance of the jejunal folds.

appearance of the small intestine in sprue from study to study or even during the course of a single examination may occur. In this study there is a discrepancy between the degree of clinical improvement under therapy and the roentgen changes observed. In only a few instances did the sprue pattern lessen in intensity or disappear.

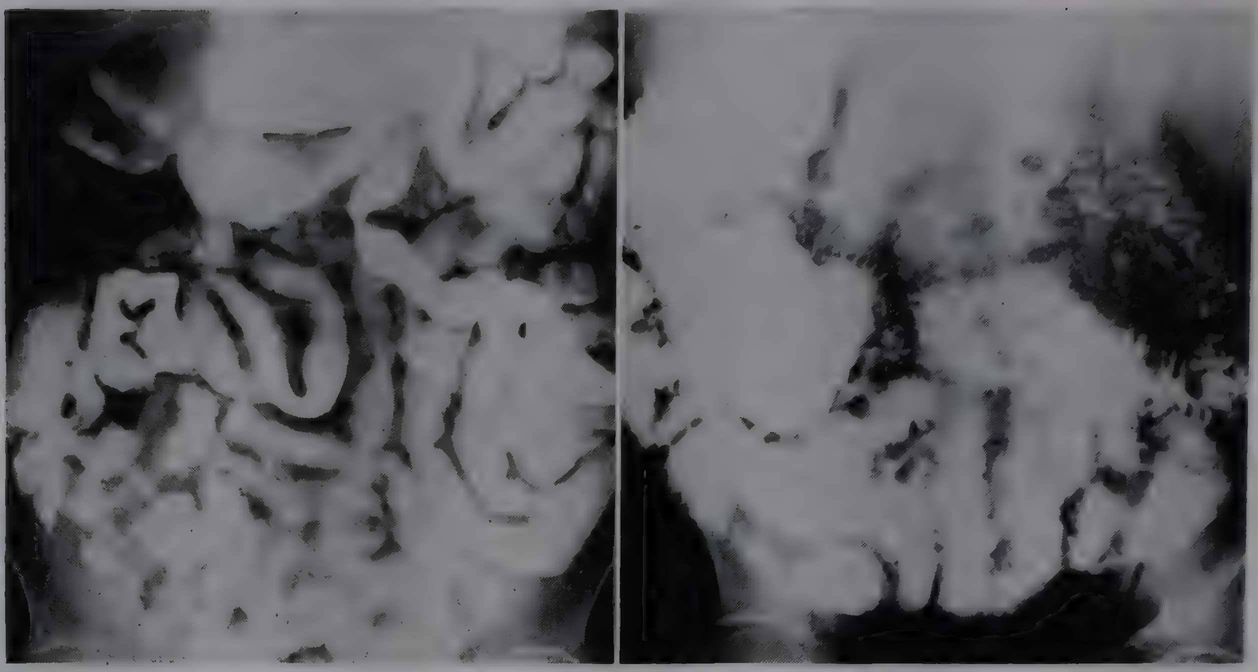


FIG. 8A FIG. 8B

FIG. 8A. Moulage phenomenon characterized by absence of mucosal folds and smooth contours of the bowel lumen. Secretions are increased. The necropsy findings, including the small intestine, were normal. Clinically, the patient was considered to have idiopathic sprue.

FIG. 8B. Whipple's disease. Slight dilatation of the mid-jejunum with thickening of the valvulae conniventes. Minimal scattering in the proximal jejunum. Later films showed segmentation, delayed type.

In four of seventeen patients maintained on liver therapy, vitamin B_{12} or folic acid, the small intestinal pattern returned to normal (Figs. 6A and 6B). Of 22 patients with abnormal small bowel studies receiving steroid therapy, two showed considerable diminution in dilatation and segmentation (Figs. 7A, 7B, 7C). In two others, segmentation and hypersecretion were reduced; however, dilatation persisted. We have had no experience with the effect of a gluten-free diet on the roentgen appearance of the small intestine.

SECONDARY SPRUE

The majority of cases of the malabsorption syndrome are due to idiopathic sprue. There are, however, several groups of diseases which give rise to symptomatic or secondary sprue.

Lymphosarcoma. Most cases of lymphosarcoma do not produce the sprue pattern nor are they associated with the clinical findings of malabsorption. Occasionally there is diffuse infiltration of the submucosa of the small intestine and mesenteric lymphatics producing a sprue syndrome with steatorrhea, excessive fatty acids in the stools and other laboratory evidences of malabsorption (28, 11). In six of 42 patients with lymphosarcoma involving the small intestine, this situation prevailed. In each case, initially, the clinical impression was sprue. Only subsequently at laparotomy or post-mortem examination did the diagnosis of lymphosarcoma become apparent.

The roentgen findings in these six patients were as follows: In four cases, the sprue pattern was seen with segmentation, dilatation, hypersecretion and scat-

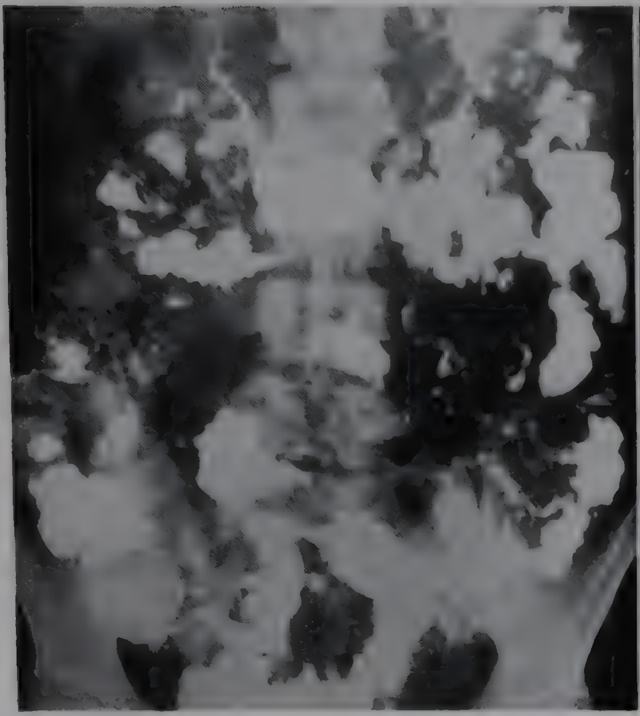


Fig. 9A

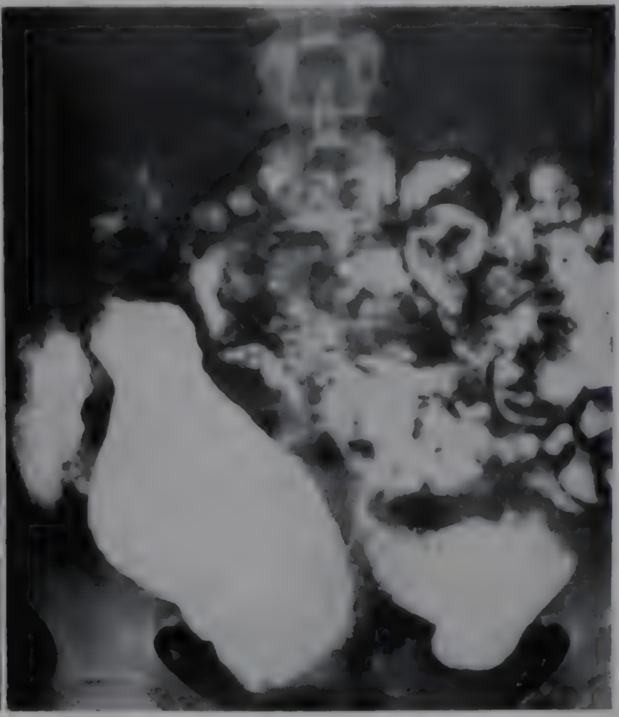


Fig. 9B

Fig. 9A. Sprue pattern in lymphosarcoma of the small intestine.

Fig. 9B. Lymphosarcoma of the small intestine with thickening of the bowel wall of the dilated segments.

tering (Fig. 9A). In two patients, in addition to the above findings, there was thickening of the bowel wall suggesting infiltration with tumor (Fig. 9B). It is of interest to note that the sprue pattern was seen only in those patients with marked steatorrhea and increased fatty acids in the stools.

Whipple's disease. Four patients were studied. In three patients, there was clinical evidence of severe malabsorption and, after prolonged observation, the diagnosis of Whipple's disease was made either after biopsy or necropsy. The roentgen findings in these patients were those of the sprue pattern (Fig. 8B). In the fourth patient, who had diarrhea without significant steatorrhea or other evidences of malabsorption, the small intestine, on roentgen study, appeared normal. Again, it is noted that the sprue pattern was seen only in the presence of marked steatorrhea and excessive fatty acids in the stools.

PANCREATIC DISORDERS

In contrast to the marked alterations in the appearance of the small bowel in primary and some cases of secondary sprue, namely Whipple's disease and lymphosarcoma, the roentgen findings in pancreatogenous steatorrhea are essentially normal. On occasion, minimal dilatation of the small intestine may be seen. In one case, slight segmentation was noted. This was in a patient with far advanced carcinoma of the pancreas and carcinomatosis. The lack of changes in the small intestine in pancreatic disorders associated with steatorrhea and malabsorption has been documented in the literature (9).

DIFFERENTIAL DIAGNOSIS

Differentiation should be made between the so-called functional disorders of the small intestine and certain organic diseases. Of these, regional enteritis is the most important. The inflammatory changes in regional enteritis occur early, are usually severe and extensive. The rigidity of the mucosal folds and lack of distensibility of the bowel lumen indicate the inflammatory infiltrate in the bowel wall. Mucosal ulceration and pseudopolyp formation further attest to the inflammatory nature of the disease process. Delayed segmentation is not seen. Dilatation is not a feature until obstruction supervenes. The involved bowel segments are separated from one another and the remainder of the intestine due to thickening of the bowel wall and intervening mesentery (Figs. 10A and 10B). Regional enteritis may cause malabsorption with steatorrhea; however, the sprue pattern has not been observed in our cases.

Amyloidosis involving the small intestine is uncommon. Thickening and fixation of the mucosal folds by amyloid deposits in the intestinal wall can occur. In one case, thickening of the folds was noted associated with hypersecretion and mild dilatation of the bowel lumen. The roentgen differentiation from sprue, in this instance, could not be made.

Scleroderma may produce small intestinal alterations manifested by dilatation, sacculation and marked hypomotility. In two cases observed, the dilatation of the second and third portions of the duodenum was especially striking. When the disease is sufficiently advanced to produce intestinal changes, the esophageal alterations are characteristic and the roentgen diagnosis is more apparent.

Malabsorption and a sprue-like pattern have been reported subsequent to subtotal gastrectomy (29). On roentgen study in our cases, a normal small intestinal pattern was generally found. A sprue pattern was a most unusual finding. Several patients were observed who showed some small intestinal dilatation following vagotomy with and without subtotal gastric resection; however, segmentation, hypersecretion and other features of the sprue pattern were not seen. In most cases, the dilatation was transient and did not persist following the initial studies.

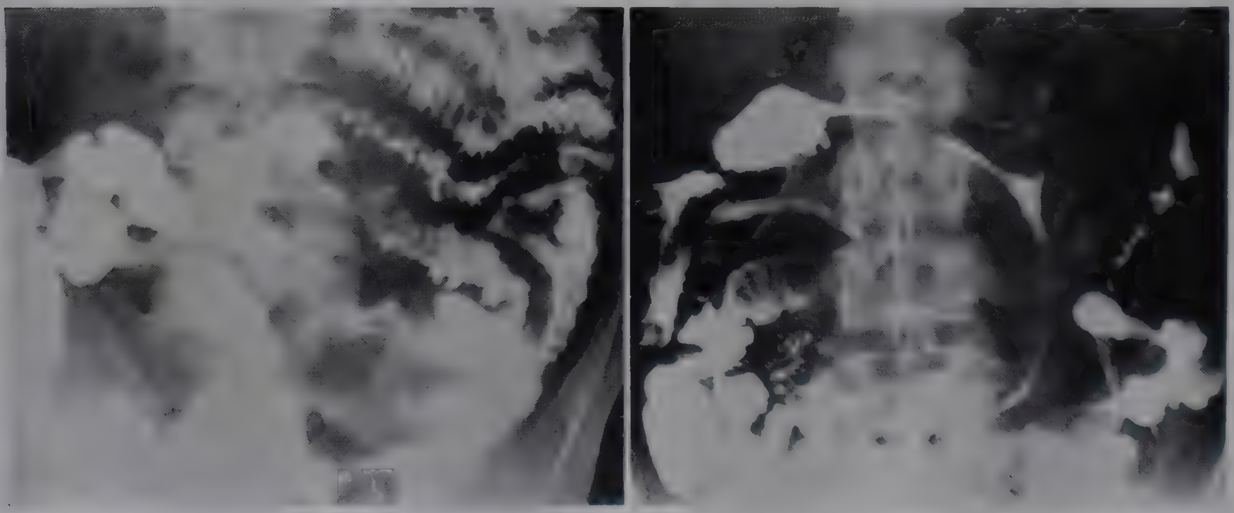


FIG. 10A FIG. 10B

FIG. 10A. Non-stenotic form of ileojejunitis. The loops of intestine appear straightened and uncoiled. The folds are thickened, blunted and in some areas, fused.

FIG. 10B. Stenotic type of ileojejunitis. The entire small bowel is involved by alternating areas of constriction and dilatation. The bowel loops are markedly separated.

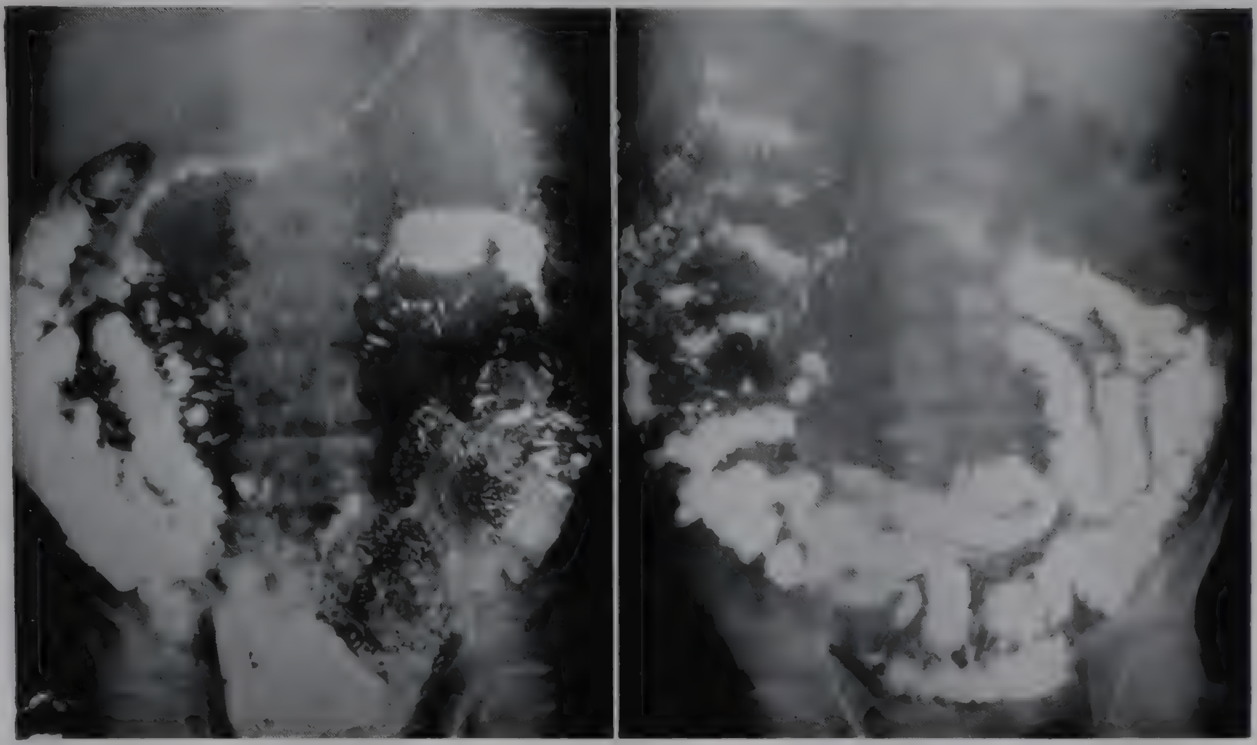


FIG. 11A FIG. 11B

FIG. 11A. and 11B. Same patient. Minimal dilatation, increased secretions. Slight segmentation and slight thickening of the mucosal folds. The roentgen findings simulate those seen in mild sprue. This patient had toxic hepatitis.

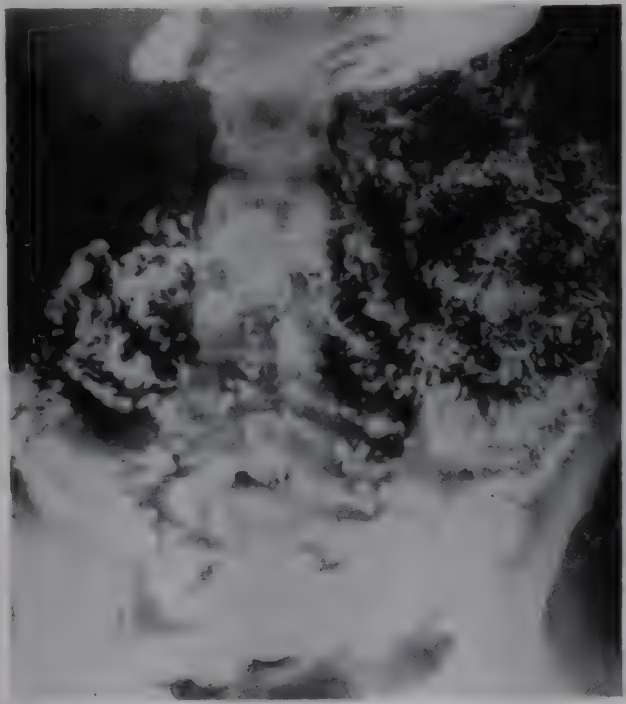
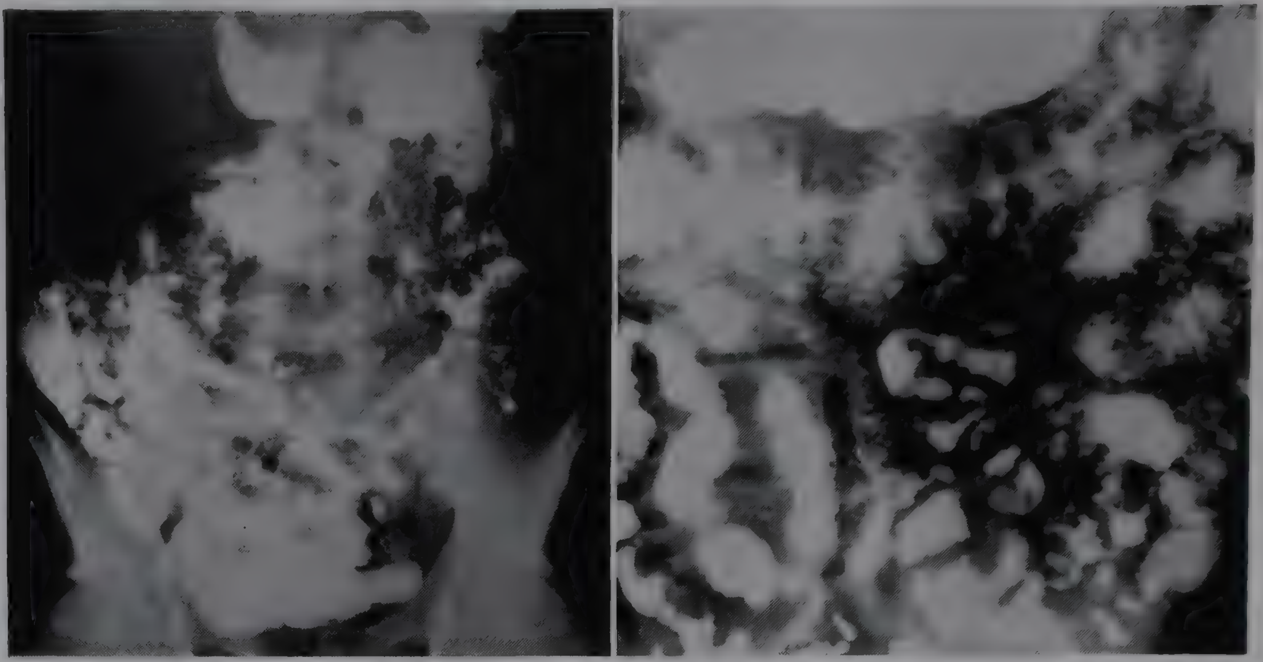


FIG. 11C

FIG. 11C. Increased secretions producing irregular distorted mucosal folds and scattering of the barium column in a patient with mild idiopathic sprue.

Not every patient with sprue shows the marked changes described above. When the changes are mild, the combination of findings of minimal dilatation, delayed segmentation and hypersecretion are still highly suggestive of sprue; however, other diseases of malabsorption, associated with defective fat metabolism, such as cirrhosis of the liver, toxic hepatitis, biliary tract disease, etc. must be included in the differential diagnosis (Figs. 11A, 11B, 11C).



FIG, 12A FIG. 12B

FIG. 12A. Thickening and some distortion of the mucosal folds with increased secretions in a patient with allergy.

FIG. 12B. An interrupted column of barium in the small intestine simulating segmentation. Increased secretions. This patient had pyloric obstruction secondary to a duodenal ulcer with intermittent gastric emptying and increased secretions.

The individual components of the minimal sprue pattern, when found alone, are seen not infrequently and are, in themselves, not diagnostic of any specific condition. For example, slight coarsening of the mucosal folds may be seen in allergy (Fig. 12A) and hookworm infestation. Dilatation can be seen following Banthine medication or after vagotomy. Minimal segmentation may occur with pyloric obstruction because of slow intermittent gastric emptying (Fig. 12B) or following administration of small quantities of barium. It may also be seen in emotional disturbances. When the roentgen changes in the small intestine are limited to these minimal alterations, they are difficult to differentiate from one another as they present no obvious distinguishing features and no roentgen diagnosis, as such, can be made.

DISCUSSION

One of the most important roentgen findings associated with the malabsorption syndrome is segmentation of the barium column in the small intestine. The nature of the production of segmentation has been the subject of considerable speculation since it was first described. It was originally considered to be part of an inflammatory process associated with idiopathic steatorrhea, then, as a result of damage to the intramural nervous system of the small intestine or an abnormality in the muscle coat. Many attempts were then made to produce segmentation by the introduction of various foodstuffs into the small intestine. Recently a pattern of segmentation was produced by the addition of mucus, fatty acid and hypertonic solutions into the small intestine. Segmentation was shown to be due to flocculation of barium within the mucus secretions and could be prevented by using special "non-flocculating" barium mixtures.

If our definition of segmentation is adhered to, namely, segmental distribution of the barium column in discrete masses with hypersecretion and dilatation of the bowel lumen, it is seen only in those cases with severe steatorrhea in which the lipid content of the stool is due to a large amount of fatty acids and neutral fats. It is generally agreed that patients with pancreatic steatorrhea have a normal small intestinal pattern. Steatorrhea, therefore, in itself, would not appear to be the cause of segmentation. However, the lipid content of the stool in sprue and pancreatogenous steatorrhea differ. In the latter, it is due to neutral fats only, occasioned by the absence of the hydrolizing effect of pancreatic lipase. In sprue, Whipple's disease and those cases of lymphosarcoma associated with steatorrhea, the fat content of the stool is made up of neutral fats and fatty acids. Fatty acids are highly irritating substances and may cause the over-secretion of mucus noted in the intestinal tract.

Although the increased fatty acids and over-production of mucus in the small intestine are probably the major factors, they do not account completely for the presence of segmentation. In patients with sprue, treated successfully, fatty acids in the stools may be returned to normal values; however, segmentation still may persist. One can speculate, then, on what factor or factors continue the production of segmentation. Is it continued hypersecretion of mucus caused by an altered intestinal mucosa? Is it related to abnormal water absorption from the small intestine or to a visceral autonomic nervous system imbalance as shown by Ingelfinger and Moss? Although all these factors may play a role, it appears that the abnormal quality and quantity of the secretions in the intestine caused by the increased fatty acids is the most important single factor in the production of the segmentation pattern.

The mechanism of production of functional changes in the small intestine has been little understood and all variations in the appearance of the small bowel which were considered functional were grouped under the term "deficiency pattern." The inclusion of so many disorders, often because of the presence of one roentgen variation, has caused such a dilution of the term deficiency disorder that it has lost its meaning. It has been recognized for many years that deficiency no longer is the basic factor responsible for the changes. The continued use of this term has prevented the recognition of specific patterns within this all inclusive group. The studies made in this series of patients suggest that the roentgen appearance, when characteristic, is usually associated only with marked steatorrhea (fatty acids) and is most frequently seen in idiopathic steatorrhea (sprue). It is suggested, therefore, that the term "sprue pattern" be utilized for these severe functional alterations. The sprue pattern may also be seen with a slightly lesser intensity in secondary steatorrhea (Whipple's disease and lymphosarcoma).

When minimal functional changes occur in the small intestine, they may be caused by malabsorptive disease. However, these changes are not specific and can also be caused by other diseases unrelated to malabsorption. In describing these abnormalities, it is suggested that an all-inclusive term such as pattern be avoided and a description only be reported by the radiologist.

ACKNOWLEDGMENT

Acknowledgment is made of permission to reproduce Figures 1B, 3A, 3B, 4A, 4B, 5A, 5B, 6A, 6B, 7A, 7B, 7C, 9B, 10A, which appeared in *Gastroenterology*, 26: 548, 1954, and in *Am. J. Roent.*, 72: 380, 1954 and Figure 1A, *Gastroenterology* 26: 548, 1954, and Figure 12A, *Am. J. Roent.*, 72: 380, 1954.

REFERENCES

1. Golden, R.: Radiologic Examination of the Small Intestine. Philadelphia. J. B. Lippincott Co., 1945.
2. Pillai, M. J. S., and Murthi, K. N.: Radiological Signs in Cases of Sprue: A Study of Nine Cases. Indian J. Med., 12: 116, 1931.
3. Bennett, T. I., Hunter, D., and Vaughan, J. M.: Idiopathic Steatorrhea (Gee's Disease). Quart. J. Med., 1: 603, 1932.
4. Mackie, T. T.: Nontropical Sprue. Med. Clin. No. Amer., 17: 165, 1933.
5. Snell, A. M., and Camp, J. D.: Chronic Idiopathic Steatorrhea, Roentgenologic Observations. Arch. Int. Med., 53: 615, 1934.
6. Mackie, T. T., Miller, D. K., and Rhoads, C. P.: Sprue: Roentgenologic Changes in the Small Intestine. Am. J. Trop. Med., 15: 571, 1935.
7. Mackie, T. T., and Pound, R. E.: Changes in the Gastrointestinal Tract in Deficiency States. J. A. M. A., 104: 613, 1935.
8. Pendergrass, E. P., and Comroe, B. I.: Roentgen Study of the Gastrointestinal Tract in Chronic Idiopathic Adult Tetany. Am. J. Roent., 33: 647, 1935.
9. Bjerkelund, J., and Husebye, O. W.: The Clinical and Roentgen Findings in Steatorrhea of Varying Etiology. Am. J. Dig. Dis., 17: 139, 1950.
10. Gutzeit and Kuhlbaum: Uber die Darmmotilitat beim Ikterus. Munchen Med. Wchnschr., 81: 1095, 1934.
11. Sleisinger, M. H., Almy, T. P., and Barr, D. P.: The Sprue Syndrome Secondary to Lymphoma of the Small Bowel. Am. J. Med., 15: 666, 1953.
12. Fries, J. H., and Mogil, M.: Roentgen Observations in Children with Gastrointestinal Allergy to Foods. J. Allergy, 14: 310, 1943.
13. Wing, W. M., and Smith, C. A.: Spontaneous and Induced Sensitivity to Foodstuffs: X-ray Studies of the Small Intestine in Man and Guinea Pig. J. Allergy, 14: 56, 1942.
14. Lepore, M. J.: Whipple's Intestinal Lipodystrophy. Am. J. Med., 17: 160, 1954.
15. Mendes-Ferreira, A. E., and Bargen, J. A.: So-called Nontropical Sprue associated with Tuberculosis of the Lymph Nodes. Proc. Staff Meet. Mayo Clin., 12: 289, 1937.
16. Kantor, J.: The Roentgen Diagnosis of Idiopathic Steatorrhea and Allied Conditions. Am. J. Roent., 41: 758, 1939.
17. Golden, R.: Abnormalities of the Small Intestine in Nutritional Disturbances: Some Observations on their Physiologic Basis (Carmen Lecture). Radiology, 36: 262, 1941.
18. Sussman, M. L., and Wachtel, E.: Factors Concerned in Abnormal Distribution of Barium in the Small Bowel. Radiology, 40: 128, 1943.
19. Sussman, M. L., and Wachtel, E.: Granulomatous Jejuno-ileitis. Radiology, 39: 48, 1942.
20. Ingelfinger, F. J., and Moss, R. E.: The Motility of the Small Intestine in Sprue. J. Clin. Invest., 22: 345, 1943.
21. Pendergrass, E. P., Ravdin, I. S., Johnston, C. G., and Hodes, P. J.: The Effect of

Foods and Various Pathological States on Gastric Emptying and the Small Intestinal Pattern. Radiology, 26: 651, 1936.

22. Frazer, A. C., French, J. M., and Thompson, M. D.: Radiographic Studies Showing the Induction of a Segmentation Pattern in the Small Intestine in Normal Human Subjects. Brit. J. Rad., 22: 123, 1949.
23. Ardran, G. M., French, J. M., and Mucklow, M. B.: Relationship of the Nature of the Opaque Medium to the Small Intestine Radiographic Pattern. Brit. J. Rad., 23: 697, 1950.
24. Adlersberg, D., Marshak, R. H., Colcher, H., Drachman, S. R., Friedman, A. I., and Wang, C.: The Roentgenologic Appearance of the Small Intestine in Sprue. Gastroenterology, 26: 548, 1954.
25. Golden, R.: Abnormalities of the Small Intestine in Nutritional Disturbances. Radiology, 36: 262, 1936.
26. Marshak, R. H., Wolf, B. S., and Adlersberg, D.: Roentgen Studies of the Small Intestine in Sprue. Am. J. Roent., 72: 380, 1954.
27. Fisher, R. B., and Parsons, D. S.: Absorption from Surviving Intestine. J. Physiol., 110: 36, 1949.
28. Fritzche, R.: Syndrome of Symptomatic Sprue in Lymphosarcomatosis of the Small Bowel and of the Mesenteric Lymph Nodes. Schweiz. Med. Wchnschr., 73: 442, 1943.
29. Glazebrook, A. J.: Functional Disorders of the Small Bowel after Gastrectomy and Vagotomy; Correlation of Radiographic and Kymographic Studies. Lancet, 1: 895, 1952.

MANAGEMENT OF PATIENTS WITH MALABSORPTION SYNDROME

HENRY COLCHER, M.D.
AND
DAVID ADLERSBERG, M.D.
New York, N. Y.

Treatment of patients with malabsorption syndrome is essentially empirical. Increased knowledge of the fundamental defects may very well lead to a more etiologic approach in the future. It may be stated, however, that present therapy is fairly satisfactory in as much as we have means of correcting, at least to a certain extent, all major manifestations of the disorders grouped under this heading and obtain satisfactory rehabilitation in a great number of patients. In some patients clinical improvement amounting to a "cure" is attained, especially in the tropical variety of sprue or in children with the celiac syndrome. In others, i.e., in patients with non-tropical sprue, complete hematologic remission may be obtained while diarrhea with or without associated symptoms of one or another deficiency may persist and require continuous medication for control.

Primary malabsorption syndrome as seen in idiopathic sprue, tropical and non-tropical, as well as celiac disease of childhood, represents a complex metabolic disorder. It is characterized by diarrhea, steatorrhea, weight loss, anemia and numerous other manifestations resulting mainly, but not exclusively from impaired intestinal absorption. The importance of the dietary management of this disorder has been stressed by many authors, as far back as Gee in 1888 (1). Clinical experience has led gradually to the use of a low fat and high protein diet (2). It became evident that some carbohydrates are better tolerated than others, i.e., monosaccharides are better tolerated than polysaccharides (starches). Thus the standard sprue diet included large quantities of strawberries and bananas (3, 4). Some authors eliminated cereals and obtained excellent results in celiac disease (5). In recent years emphasis has been focused on the gluten content of wheat and rye (6). Gluten-free starch is apparently well tolerated. Details of the development of this knowledge will be given in the section on dietary management.

Other specific measures for the treatment of sprue have been searched for. It appears that physicians in China and in Ceylon knew many centuries ago of the usefulness of liver in the treatment of sprue. In 1927 after the introduction of liver therapy for pernicious anemia, Bloomfield and Wycoff treated similarly a case of sprue with macrocytic anemia and observed excellent clinical improvement (7). Crude liver extract appears to be superior to the highly purified liver preparations (8). Since their introduction, folic acid and vitamin B_{12} have been used extensively. Folic acid appears to be more effective in patients with tropical sprue (9). Similar results have been reported with folinic acid (10).

From the Nutrition Clinic and The Department of Medicine, The Mount Sinai Hospital, New York, N. Y.

In patients with non-tropical sprue the clinical response to the dietary management supplemented by the above described drugs may result in correction of the anemia and variable control of other manifestations of the malabsorption syndrome. There are, however, numerous patients in whom this control is not adequate. Additional measures are then employed, such as the administration of calcium, iron and potassium salts, vitamin B complex, vitamins C, D or K. At times antibiotics have been used with good results especially in the tropical variety (11). Other measures, such as transfusions or the administration of serum albumin or plasma may be life saving.

In refractory cases, responding poorly or only partially to the above described measures, the administration of corticosteroids or corticotropin has induced a clinical remission in the majority of patients observed by us and independently by others (12–18). The plan for management of patients with idiopathic sprue which is used at The Mount Sinai Hospital will be described.

DIETARY MANAGEMENT

Since the major manifestations in the malabsorption syndrome are related to impaired handling of fat and polysaccharides, the basic regimen consists of a high-protein, low-fat diet with moderate amounts of carbohydrates preferably given as monosaccharides. It centers around lean meat, egg whites, cottage cheese, skimmed milk, bananas and strawberries. The amount of food is gradually increased in proportion to the patients' tolerance. To avoid monotony it is imperative to guide the patient and teach him to prepare a variety of combinations of the above simple ingredients to obtain more normal appearing meals. A good selection of recipes can be found in an article previously published from this hospital (19).

High protein appetizers can be prepared by adding two tablespoons of cottage cheese or egg whites to tomato juice, by blending chopped liver with an egg white and tomato juice, or by preparing dishes consisting of cottage cheese, bananas and melba toast crumbs.

Soups can be enriched with egg white, Parmesan cheese or ground beef. Sea food chowders can be made with skim milk, oysters, clams or mussels.

Lean meats and fish should be chosen and trimmed to keep the fat as low as possible. Meat, fish and poultry can be broiled, boiled or roasted. Combinations of ground beef, banana flakes and cottage cheese make an appetizing meat loaf.

Vegetables and salads should be low in carbohydrates. Frozen and molded salads can be prepared with cottage cheese and gelatin.

Desserts can be prepared using bananas and strawberries with gelatin, egg white or cottage cheese. Creamy type puddings can be prepared with skim milk and the allowed fruits. Saccharin, lemon juice, vanilla or other flavors can be used to make these dishes more attractive.

As the general condition improves more food items are introduced, leading gradually to a bland type of diet. But even then it is important to avoid consumption of large amounts of fat or cereals.

GLUTEN-FREE DIET

A new approach to the dietary management has evolved in the past few years. Studies in Holland (20), confirmed by observations in England (21–23) and in this country (24), have led to the observation that, in a great number of children with celiac disease and a certain number of adults with sprue, good clinical control has been achieved with gluten-free diets that contain otherwise liberal amounts of fat and starch. The deleterious effect of wheat flour was attributed to its gluten content and more specifically to the gliadin fraction. The administration of wheat starch (free of gluten) did not result in any harmful effect. This approach seemed to be less successful in adults with sprue. The question has been raised whether all clinical entities grouped under the heading of idiopathic sprue represent the same basic defect. One may reason that some patients have a specific sensitivity to gluten and will respond favorably to the elimination of this element. This diet has the advantage of increased variety since the only foods to avoid are the wheat and rye products. Obviously great care is needed to ascertain that even small amounts of such foods are avoided. Carbohydrates may be taken in form of bread made with wheat starch (gluten-free), rice flour, corn meal, potato starch or soy beans. There are numerous cereals on the market made with corn or rice to allow variety. The diet includes all fruits, vegetables and juices, all meats and meat substitutes as well as liberal amounts of fat. Desserts may be made of fruits, corn starch, rice, tapioca, custard, gelatin and sherbets. Some authors allow milk and ice cream. Our experience with this type of diet is limited but good results have been reported by many authors (21–24). Table I presents list of foods allowed and to be avoided in the gluten-free diet and Table II shows a sample menu.

DRUG THERAPY

Certain drugs have become an essential part of the management of patients with malabsorption syndrome.

Liver extract, preferably the crude preparation, is given parenterally. It must be given in larger doses than for pernicious anemia, 2 to 4 ml. daily by intramuscular route during the acute phase of relapse, later on once or twice weekly depending on the clinical improvement.

Folic acid can be administered both orally and/or parenterally in doses of 10 to 30 mg. daily. Although it appears to be extremely useful and can control the anemia and the diarrhea of patients with tropical sprue, it should be used very cautiously in patients with lesions of the central nervous system. Large doses of vitamin B_{12} should be given simultaneously.

Folinic acid (leucovorin, citrovorum factor) is effective during the acute phase in intramuscular doses of 3 mg. daily. It may be followed by weekly injections of the same dose after clinical improvement is achieved.

Vitamin B_{12} can result in striking hematologic and clinical response in doses of 100 μg. given parenterally. Maintenance doses of 30 μg. weekly are often sufficient to maintain a satisfactory hematic control. In the presence of central nervous system involvement daily parenteral doses of 1 mg. are indicated.

TABLE I

Gluten-free diet

This diet is free from cereal proteins except those found in rice and corn

Foods Allowed	
Milk	Two glasses or more, flavored if desired, more for children.
Eggs	One to two a day.
Meat, fish, or poultry	Two medium servings daily (not breaded, creamed or served with thickened gravy, or bread dressings otherwise prepared as desired).
Cheese	As desired.
Bread	Made from rice, corn, soy bean and gluten-free wheat flour only. Popcorn, potato chips, Fritos, Cheetos.
Cereals	Corn flakes, cornmeal, hominy, rice, Rice Krispies, Puffed Rice, Sugar corn pops.
Fat	Margarine, true mayonnaise without wheat products, butter, all oils except wheat-germ oil.
Vegetables, potatoes	As desired, except creamed. Rice may be substituted occasionally for potatoes.
Fruits	As desired.
Soups	All clear and vegetable soups; cream soups thickened with cream, cornstarch or potato flour only.
Desserts	Jello, fruit Jello, ice or sherbet, homemade icecream, custard, Junket, rice pudding, cornstarch pudding (homemade) or *blanc mange* if thickened with cornstarch.
Beverage	Milk, fruit juices, ginger ale, cocoa, coffee (made from ground coffee), tea, carbonated beverages.
Sweets	Sugar (white or brown), molasses, jellies and jams, honey, corn syrup.

Foods Omitted	
Meat, fish and poultry	Meat patties or meat loaf made with bread or bread crumbs, croquettes, breaded meats, fish or chicken, bread stuffing, chili con carne and other canned meats, cold cuts unless guaranteed pure meat.
Gravies, sauces	All gravies or cream sauces thickened with wheat or rye flour.
Bread	All bread, rolls, crackers, cake and cookies made from wheat or rye; Ry-Krisp, muffins, biscuits, waffles, pancake flour and other prepared mixes, rusks, zweiback, pretzels, other products containing oatmeal, barley or buckwheat; breaded foods, bread crumbs.
Cereals and cereal products	All wheat and rye cereals, wheat-germ, barley, oatmeal, buckwheat (kasha), noodles, macaroni, spaghetti, dumplings.
Fats	Commercial salad dressings except pure mayonnaise.
Vegetables	Any prepared with cream sauce or breaded.
Soups	All canned soups except clear broth; all cream soups unless thickened with cream, cornstarch or potato starch.
Desserts	Cakes, cookies, pastry, puddings and commercial ice cream; All homemade puddings thickened with wheat flour.
Beverages	Postum, malted milk, Ovaltine, instant coffee, beer, ale
Sweets	Commercial candies containing cereal products.

WARNING: Check all labels for presence of wheat or rye flour.

TABLE II

Sample Menu

Meal Plan		Servings	
		Weight (gm.)	Household measure
		Breakfast	
Fruit	Orange	100	1 medium
Egg	Soft cooked	50	1
Cereal	Corn flakes	20	1 serving
Milk	Milk	240	1 glass
Bread	Rice bread	20	1 slice
Butter	Butter	5	1 pat
Coffee	Coffee	200	1 cup
Milk	Milk	60	1 pitcher
Sugar	Sugar	15	1 tablespoon
		Luncheon	
Soup	Clear broth	150	1 cup
Protein dish	Cottage Cheese	60	¼ cup
Salad	Lettuce	30	2 leaves
	Tomato	100	1 medium
Dressing	French dressing	6	2 teaspoons
Bread	Rice bread	40	2 slices
Butter	Butter	10	2 pats
Beverage	Milk	240	1 glass
Dessert	Custard	100	1 cup
		Dinner	
Meat	Roast beef	90	3 ounces
	Pan gravy	30	2 tablespoons
Potato	Potato	100	1 medium
Vegetable	Baked squash	100	1 serving
	Spinach	75	1 serving
Bread	Rice bread	20	1 slice
Butter	Butter	10	2 pats
Dessert	Homemade ice cream	60	1 serving
Beverage	Coffee	200	1 cup
Milk	Milk	60	1 pitcher
Sugar	Sugar	15	1 tablespoon

Vitamin B concentrates in form of injections of vitamin B complex are often useful. Oral administration may, however, give excessive bloating.

Iron therapy is indicated in patients with microcytic hypochromic anemia. At times oral iron therapy may be inadequate, since the intestinal absorption of this element may be markedly impaired. Parenteral administration of adequate doses may produce dramatic results, as may be seen from the case presented in Figure 1.

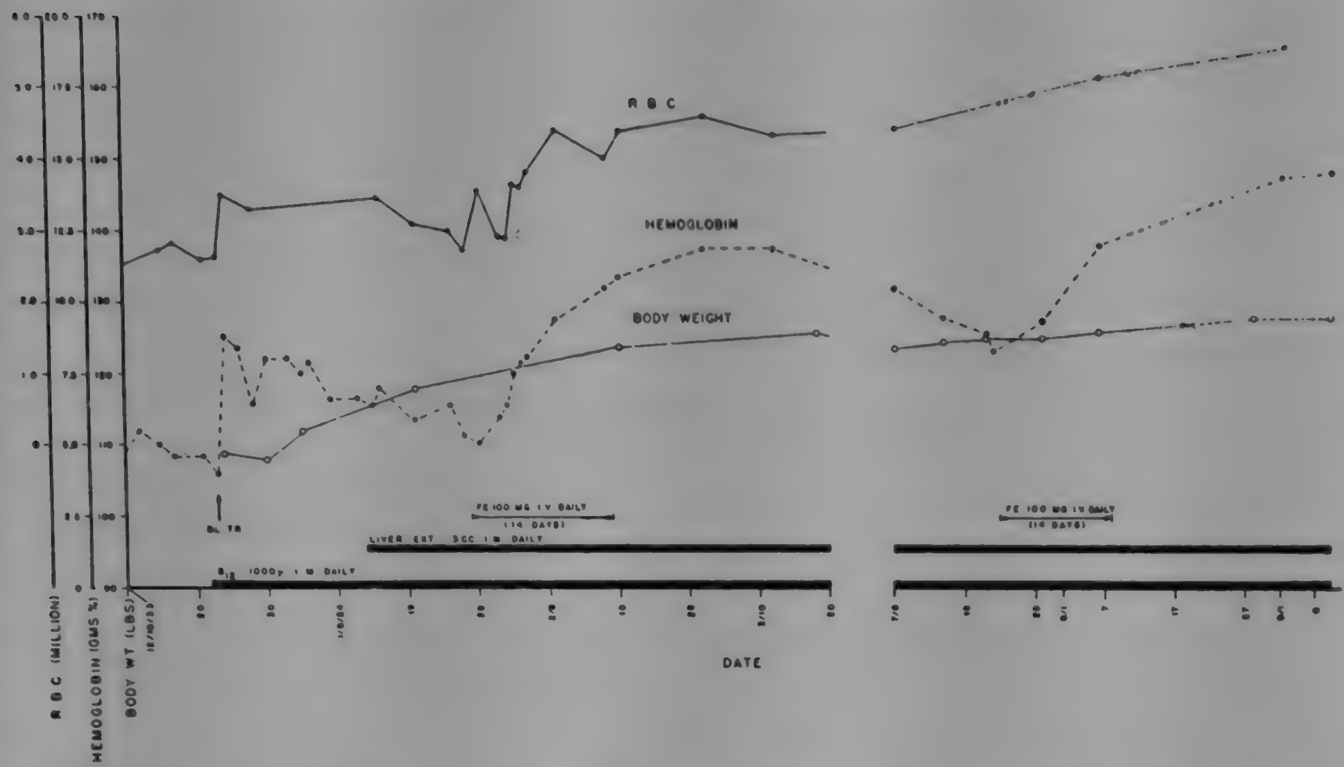


FIG. 1. Effect of intravenous iron therapy in a patient with non-tropical sprue and microcytic hypochromic anemia. Note the prompt effect of iron administration (two courses) on the blood count in contrast to that of prolonged parenteral therapy with vitamin B_{12} and liver extract. (Ref. 18)

Additional supplements must be given to patients who present other deficiencies. Hemorrhagic manifestations caused by hypoprothrombinemia respond to the parenteral administration of vitamin K. In the presence of associated hepatic damage large amounts of fresh blood may be indicated. Marked hypoproteinemia may be corrected to a certain extent by the administration of large doses of salt-free albumin or plasma. This effect is usually transient and more lasting results may be obtained by steroid therapy (see later). Hypocalcemia and tetany require administration of large doses of calcium salts, orally and/or parenterally. Osteomalacia and osteoporosis may be helped by large doses of vitamin D and testosterone. This form of therapy is discussed elsewhere in the symposium (25). Some patients, especially those with marked lassitude, may benefit from the administration of potassium salts.

Careful observation of the patient, painstaking attention to details and prolonged use of various combinations of drugs will usually result in satisfactory control of the malabsorption syndrome and allow the patient to lead a fairly normal life. A certain equilibrium may then be established that will permit the omission of some drugs for varying periods. At the slightest indication of recurrence it is essential to resume the full therapeutic program. After various periods of time some patients may develop various degree of resistance to these measures.

RESULTS OF DRUG THERAPY

Out of a larger number of patients 94 were selected for detailed analysis. The average observation period of this group was 5.2 years. Clinical data and diagnostic criteria are presented elsewhere (26). Management can be described as a systematic and gradual application of various therapeutic measures guided by the patient's response. Attempt was made at first to control the manifestations of the malabsorption syndrome by diet alone. When the symptoms and signs were severe, and this applied to the majority of our patients, additional therapeutic measures were introduced as rapidly as compatible with the principle of evaluating the efficacy of each preceding step. Only rarely, however, was the clinical picture so alarming that many drugs were given immediately and separate analysis was impossible.

The therapeutic response was recorded in the following manner: (a) remission (b) full control (c) partial control (d) no change (e) fatal termination.

Remission was defined as disappearance of all clinical manifestations, not only during the treatment period but also during a prolonged follow-up without treatment. After cessation of all medication the patient could tolerate a practically free diet. Only six patients could be placed in this group. Five of these were Puerto Ricans and one Jewish. Five had received liver extract and one was given liver extract and vitamin B_{12}. It is possible that improved dietary habits and perhaps living conditions played a significant role in maintaining clinical remission once the acute phase or the manifestations of the syndrome were brought under control.

Full control was defined as achievement of satisfactory control of all major manifestations of the malabsorption syndrome, while under continued therapy. This was observed in 32 patients. Seventeen had received liver extract with folic acid and two received vitamin B_{12} in addition to the above. Some patients of this group responded originally to the standard therapeutic regimen but became refractory to it after months or years. Others proved to be therapy-resistant from the beginning and required steroids. Corticotropin or one of the cortisones were then administered as will be discussed later.

Partial control. This group never achieved full control of all the manifestations of the malabsorption syndrome. The degree of control varied from patient to patient. At times some manifestations were fully controlled, while other evidences of malabsorption persisted. There were also fluctuations in the degree of control, perhaps related to seasons or to emotional factors not always clearly understood. This group of 37 patients was the largest in our series. The drugs used in this group were as follows: diet with only vitamin supplements in one patient; diet with vitamin supplements and liver extract in 13 patients; all these factors plus folic acid in one patient and with vitamin B_{12} in five other patients. Seventeen patients of this group were given various steroids and will be discussed later.

No change. Six patients failed to respond to the forms of therapy employed. One was treated with diet alone; two received diet with liver extract; one received folic acid in addition to these therapeutic agents and two did not respond to all these measures even when supplemented with corticosteroids.

Fatal termination. Thirteen patients died during or after their treatment at the hospital. Eight received diet with liver extract and folic acid. One received vitamin B_{12} in addition. Four received steroids, three of these were treated in the terminal stages of their disease; the fourth had responded favorably for two years but died subsequently despite continued therapy; these four cases will be discussed later.

STEROID THERAPY

The debatable role of the adrenal cortex in intestinal absorption (12) suggested the use of corticosteroid therapy in refractory cases of the malabsorption syndrome. Satisfactory results have been obtained with this form of therapy which has been used in this hospital since 1950 (12, 15, 16, 18). A total of 33 patients with refractory sprue treated with corticotropin or the cortisones have been selected for analysis. Of these, 30 patients have been observed for periods from six months to six and a half years. One patient presented elsewhere in this symposium (26) was not available for follow-up studies.

Dramatic results within a few hours have been obtained during the "acute" phase of the disease by intravenous administration of corticotropin or hydrocortisone. The usual approach was administration of relatively large doses of either cortisone, hydrocortisone, prednisone or prednisolone orally with gradual reduction in dosage depending on the clinical improvement. The initial daily dose was usually 100 mg. of cortisone, 80 mg. of hydrocortisone free alcohol and 50 to 60 mg. of prednisone or prednisolone. This was given orally in divided doses. ACTH was usually injected intramuscularly (80 to 100 mg. in two doses 12 hours apart). The initial daily dose was usually maintained for eight to ten days. Since improvement was often manifest within a few days it was possible to start reducing the dosage after the first week of therapy. This reduction was done by weekly decrements of 10 to 20 mg. until the maintenance dose was reached. The main guiding features were the number of stools, appetite, weight and well being.

Since our purpose has always been to establish the minimal dose of steroids needed to maintain clinical control, we have often "titrated" the patients by gradual reduction of the daily dose to such low levels as 15 mg. of cortisone or 5 mg. of prednisone daily, with continuous, careful observation of all symptoms and signs. In the process of "titration" recurrence of some of the manifestations of sprue was observed. It was then necessary to raise the dose of the drugs to somewhat higher levels, still remaining within "safe limits" to allow long term administration.

Table III shows the data concerning prolonged steroid therapy in 30 patients. Seven patients have been on almost uninterrupted therapy for five years or longer, six patients from four to five years, eight from three to four years, and nine patients less than three years, but not less than six months. During the initial period of steroid therapy the standard sprue diet remained unchanged, except for limitation of the salt intake to less than 2 gm. per day. The diet was then gradually liberalized to a bland mixed diet, with some limitation of fats, coarse vegetables and fruits. Supplements of calcium and potassium salts were often given. The standard anti-anemic drugs were always continued (liver extract, folic acid and vitamin B_{12}). If required, iron salts were also given orally or parenterally. With the initial larger doses of corticotropin or cortisone fluid retention was sometimes encountered and treated with mercurial diuretics. This phenomenon was seen less often with prednisone or prednisolone. On several occasions, when a patient appeared fully controlled with small doses of steroids, attempts were made to discontinue these hormones. This was followed within relatively brief periods by partial recurrence of manifestations of the malabsorption syndrome heralding the onset of relapse. Resumption of steroid therapy at a

TABLE III

Results of Steroid Therapy in 29 Patients

Case No.	Sex	Age	Duration of disease prior to observ. (yrs.)	Aver. daily maint. dose, (mg.)				Duration of therapy (mons.)	Result	Remarks
				ACTH	E	F	P			
1	M	36	2				30	14	4+	
2	F	42	16			30	10	48	4+	Tetany
3	F	30	10	60/20		50/30		70	4+	Volvulus of cecum
4	M	37	10	50	75	30	15	60	4+	Marked hypoproteinemia
5	F	39	11			40	15	60	4+	
6	M	57	2			40		45	3+	Hemiplegia
7	F	59	1	20/wk.		30	30	45	3+	Osteoporosis, tetany
8	M	43	11				10	36	4+	Combined system disease
9	F	55	1			25	10	45	4+	
10	F	37		40/20			10	36	3+	
11	F	43	2	60	50	20	10	62	4+	
12	F	60	10	50	50	20		76	3+	Hemorrhagic phenomena
13	M	40	9	20	60	40		60	3+	
14	F	41	13	40				26	4+	Diabetes
15	F		6			40		45	4+	
16	F	63	3				20/5	14	3+	Fractures
17	M	56	1				12	10	4+	
18	F	47	11	56		40	15	26	4+	
19	F	36	8	20	50	15	10	48	4+	
20	F	46	40			20		40	4+	
21	M	41				40/15	20	8	3+	Interrupted for 2 yrs.
22	F	65	2		50	20		48	4+	
23	F	60	9			40	25	48	4+	
24	M	50	17	60	75	20	15	54	4+	Osteoporosis, hemorrhagic phenomenon
25	F	28	6	40	50	40	20	78	4+	
26	F	40	7			30	7	48	4+	
27	F	41	4				10	8	4+	
28	M	26	8			40	20/15	18	4+	
29	M	35	1	50	50			36	3+	Died

E = cortisone; F = hydrocortisone; P = prednisone or prednisolone.

somewhat higher initial dose promptly controlled the recurrence. It has been our routine to interspace prolonged cortisone therapy with short courses of corticotropin in order to combat possible inactivation of the adrenal cortex. Daily injections of ACTH were used for one week or ten days. Recently we have been employing a different technique. The patient continues to take orally one of the cortisones at the established maintenance level and receives in addition weekly or bi-weekly injections of ACTH, usually 20 units. The usefulness or advantages of this approach is difficult to evaluate.

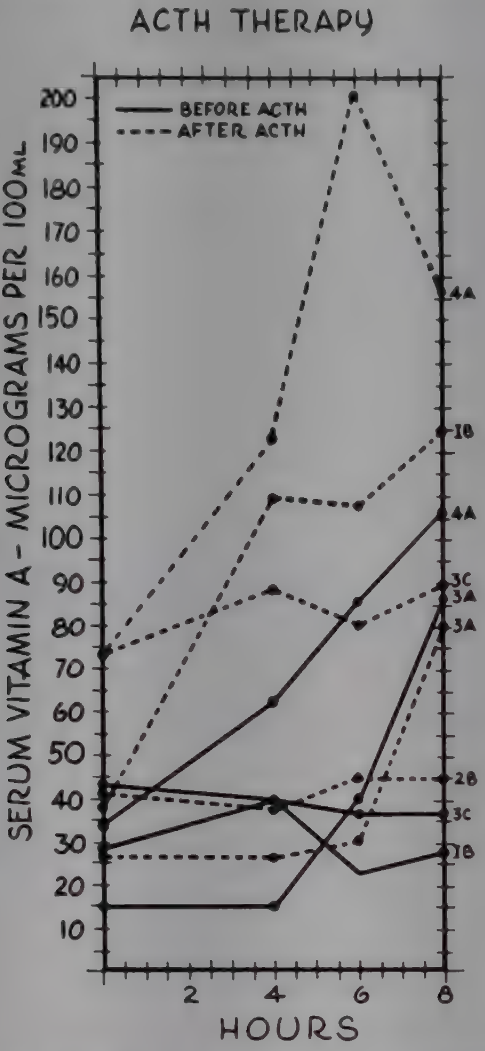


FIG. 2. The effect of ACTH therapy on vitamin A tolerance test in patients with sprue. The uninterrupted curves represent the pre-treatment tests while the interrupted curves represent the tests performed during or soon after ACTH therapy. The numbers in arabic followed by capital letters (1A, 1B) designate patient and course of therapy. No pre-treatment test was performed before course 2B (Ref. 12).

RESULTS OF STEROID THERAPY

Clinical remission was observed in 28 patients. The extent of this remission varied from patient to patient. The important clinical changes were increase in well being, increase in appetite that at times became ravenous often leading to considerable gain in body weight, the subsidence of diarrhea, and reduction in steatorrhea. There was laboratory evidence of improvement, namely, increase in serum albumin, serum calcium, fasting carotene and vitamin A levels. Improved oral dextrose tolerance tests and vitamin A tolerance tests were also noted (Fig.

2). Symptoms related to hypoalbuminemia and hypocalcemia, such as edema or tetany, disappeared with the correction of the blood abnormalities. At times radiologic evidence of improvement (disappearance of the sprue pattern) was noted. Extensive case histories and chemical and roentgen studies have been published previously (12, 15, 16, 18, 27).

For tabulation purposes patients were divided according to the over-all therapeutic response over this extended period of observation. Those who showed significant clinical and laboratory evidence of improvement for prolonged periods of time were classified as four plus. These patients were leading a normal life for all intents and purposes but had to continue the maintenance doses of one of the steroids. At times the administration of drugs was interrupted for several weeks, but signs of relapse necessitated resumption of steroid therapy. They could tolerate a practically free diet and pursue their occupations. A total of 20 patients were considered to belong in this group.

The results obtained in eight patients were classified as three plus. Despite good clinical improvement they were more apt to show minor symptoms or signs of relapse either after some food indiscretion or after too rapid a reduction in the dose of the steroid. They were easily fatigued and less able to pursue a normal life.

One patient (Case 4) was classified as two plus. His diarrhea, steatorrhea, appetite and sense of well being were fairly well corrected when given steroids, but the main manifestation of his disease, marked hypoalbuminemia, was not changed. One patient (Case 29 of Table III) died and will be discussed later.

No instance of cure or full remission was observed. Symptoms invariably recurred after various time intervals when the steroids were discontinued. Steroid therapy was discontinued at some time in all patients, but all of them relapsed and required resumption of steroids.

REPORT OF CASE

Case 25 (Table III) is presented to illustrate the long term management of a patient with non-tropical sprue. The clinical course before steroid therapy and the effects of cortisone and ACTH during 1950 and 1951 were reported previously (12). Various steroids have been employed during the past six and a half years and have resulted in the rehabilitation of this patient.

The patient, a white, Jewish woman, was born in New York City in 1921. She had never travelled abroad and gave no personal or family history of nutritional or intestinal disorders. During childhood, she was considered to be underweight and sickly and suffered from attacks of frequent epigastric pressing pains, occasionally associated with vomiting. Her growth and development was otherwise fairly normal. At the age of 17 years she reached a peak weight of 116 pounds. At age 20, on her wedding night, the patient experienced an acute attack of abdominal cramps associated with eight to ten non-bloody, watery stools. These symptoms persisted for two weeks and subsided spontaneously. Shortly after her marriage the patient became pregnant. Six weeks after delivery, in the spring of 1942, she had her second attack of abdominal cramps and diarrhea consisting of three to four loose or semi-formed, foul-smelling, non-bloody stools. This attack again lasted two weeks and subsided without specific therapy. Similar attacks occurred regularly each spring for the next five years, were associated with a weight loss of five to ten pounds and increased gradually in intensity. The diagnosis of non-tropical sprue was made in the spring of 1949 and the patient was treated with injections of liver extract, vitamin B complex and antispasmodics. In June 1949 she was hospitalized because of an acute exacerbation with marked weight loss and dehydration necessitating transfusions, glucose and saline infusions, in addition to treatment with folic acid and vitamin B_{12}. Two months later the patient was readmitted because of an exacerbation of diarrhea and the onset of amenorrhea. Her weight was 83 pounds. She appeared pale and cachectic. The abdomen was somewhat distended. There was a mild normochromic anemia. The prothrombin time was 120 seconds (control 11 seconds). The stool contained large amounts of fatty acid crystals. Serum albumin was 2.9 and serum globulin was 1.7 gm. per 100 ml. The oral glucose tolerance test revealed a flat absorption curve. Gastric analysis revealed free acid. Pancreatic secretion studies before and after the administration of secretin showed a normal volume flow and bicarbonate concentration but a somewhat reduced amylase concentration. Radiologic studies showed dilatation of several loops, segmentation and scattering of barium in the small intestine. Despite intensive and prolonged standard therapy, the patient ran a progressively deteriorating course during the next five and a half months (Fig. 3). Diarrhea persisted, ascites and leg edema appeared. Her weight fluctuated between 73 and 87 pounds. There was one episode of hypocalemic tetany and transient manifestations of purpura. Administration of

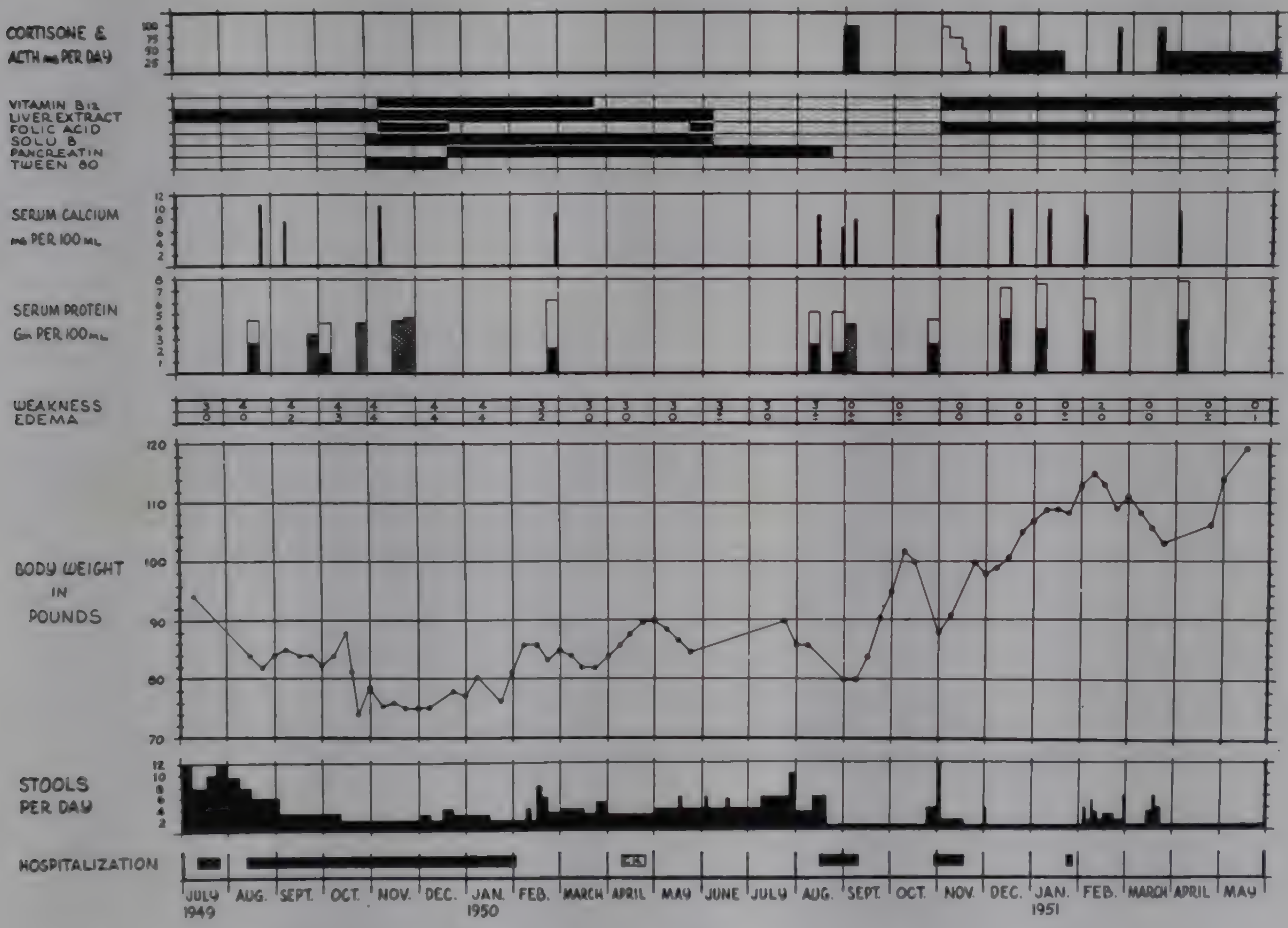


FIG. 3. The effect of ACTH and cortisone treatment on a therapy-resistant sprue patient. The white block indicates the dose and duration of ACTH administration and the black blocks indicate the dose and duration of cortisone therapy. The total serum proteins are represented by cross-hatched blocks; whenever the serum albumin and globulin fractions were determined they were represented as the black and white areas of a block respectively. C.H. represents convalescent home. ACTH and cortisone treatment resulted in a decrease in the number of stools, an increase in body weight and an improvement in the sense of well-being. Exacerbations of symptoms followed cessation of therapy. Prolonged cortisone therapy resulted in a striking weight gain and was associated with the return of the serum calcium and albumin to normal levels. (Ref. 12.)

antibiotics, Sulfathalidine and Chloromycetin had but transient beneficial effects. Because of persistence of severe symptoms and resistance to all known forms of therapy she was readmitted in August 1950 for a trial with cortisone. Clinical findings and laboratory data were similar to those observed on earlier admissions. Total fecal fat was 40.6 per cent of the dry fecal weight. Serum calcium varied from 6.5 to 8.5 mg. per 100 ml. Repeated oral glucose and vitamin A tolerance tests revealed flat absorption curves. Cortisone therapy was instituted with daily intramuscular injections of 100 mg. for ten days. Diarrhea disappeared promptly; appetite and good consumption improved, resulting in a weight gain of 23 pounds. About five weeks after discontinuation of cortisone therapy the patient had a recurrence of diarrhea with loss of 13 pounds. She was readmitted in October 1950 for a 12 day course of ACTH. Again there was a prompt disappearance of diarrhea and an increase in appetite and sense of well being with gain of 11 pounds. In December 1950, after another mild clinical relapse, the patient was started on a prolonged course of steroid therapy. This has been continued to the present (February 1957) with occasional brief interruptions. By May 1951 her weight reached 119 pounds and she was capable of performing part-time secretarial work in addition to her household duties (Fig. 4).

Frequently attempts were made to re-evaluate the patient's need for the various steroids in order to maintain good appetite, a sense of well being and regular bowel movements. At times as little as 15 mg. of cortisone daily was sufficient for extended periods. On other occasions, however, the dose had to be raised to as much as 75 mg. of cortisone daily. The larger doses were associated on occasion with marked constipation. The hemotologic status remained normal. Serum protein and calcium returned to normal values in 1951. Prothrombin concentration was kept adequate with vitamin K administered either orally or parenterally. The effect of steroid therapy on vitamin A tolerance tests is illustrated in Figure 5. The radiological appearance of the small intestinal tract was considered normal after one year of prolonged therapy, and remained so during follow-up studies. During her last admission to the hospital (November 1955) the oral dextrose tolerance test revealed

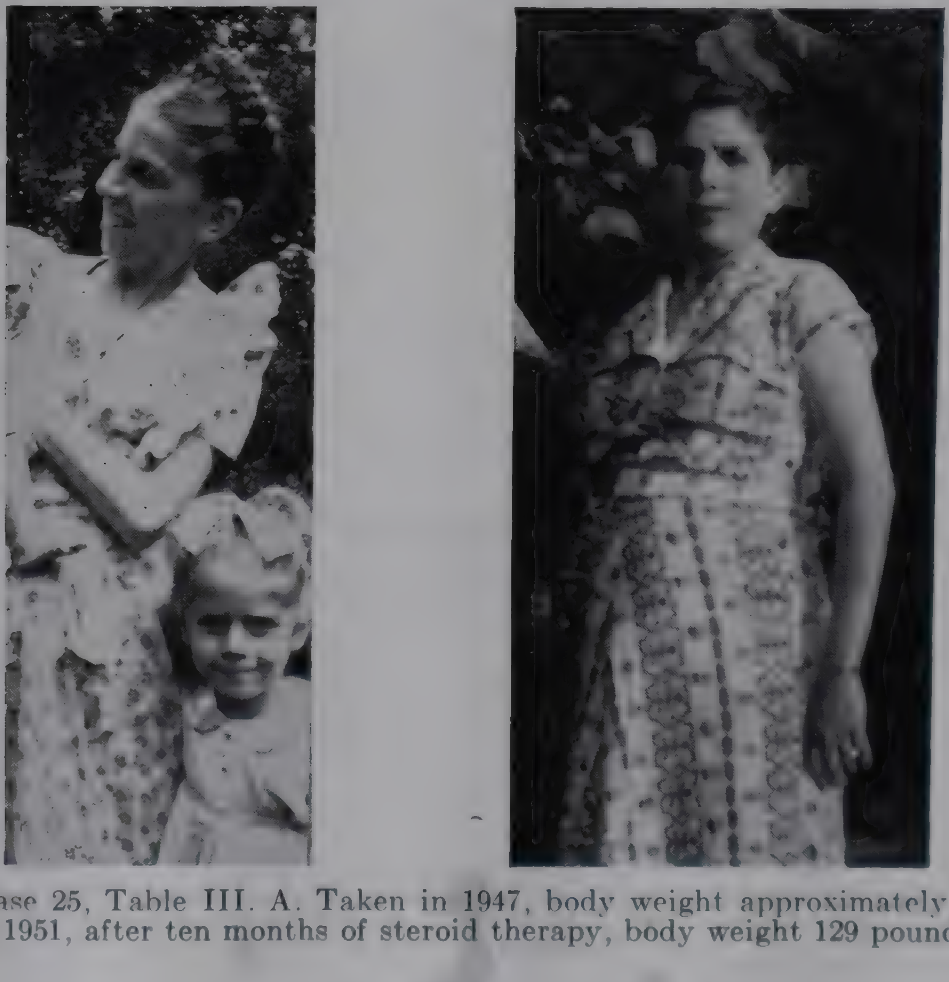


FIG. 4. Case 25, Table III. A. Taken in 1947, body weight approximately 80 pounds. B. Taken in 1951, after ten months of steroid therapy, body weight 129 pounds.

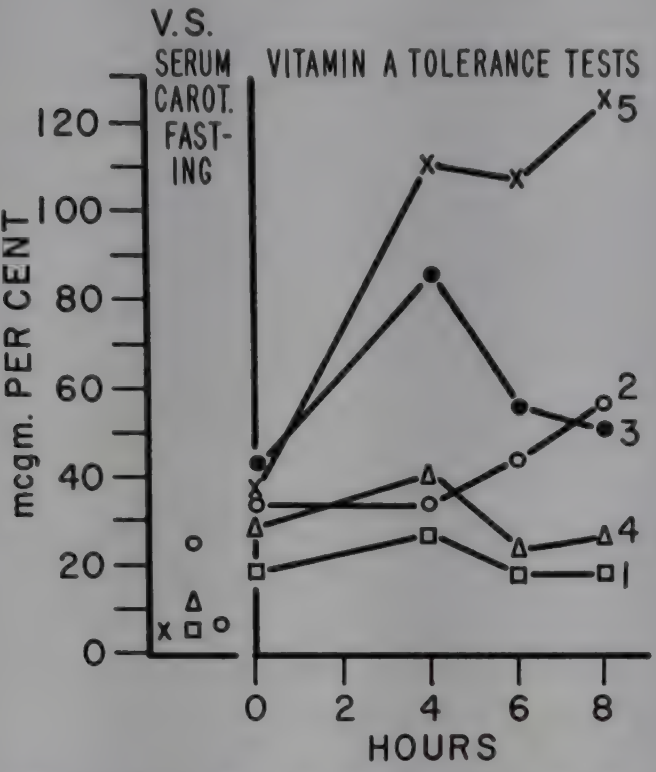


FIG. 5. Test 1 was performed on Aug. 17, 1950 before institution of cortisone therapy; tests 2 and 3 on Sept. 5, 1950 and Sept. 20, 1950 during cortisone therapy; test 4 was performed on Oct. 30, 1950 forty days after discontinuation of cortisone and prior to institution of ACTH therapy; test 5 was performed on Nov. 13, 1950 after 2 weeks of ACTH therapy.

Note improvement of vitamin A absorption under cortisone, indicated by higher serum vitamin A levels during the tolerance tests, the return to the flat curve 6 weeks after discontinuation of cortisone, and the decided improvement with ACTH.

a normal curve: 84, 126, 159, 129 and 132 mg. per 100 ml. in the fasting, 30, 60, 120 and 210 minutes specimens. The vitamin A tolerance test was normal (Fig. 5). Blood studies were as follows: serum albumin, 4.3 gm. per 100 ml.; serum globulin, 3.1 gm. per 100 ml.; serum calcium, 10.5 mg. per 100 ml.; phosphorus, 3 mg. per 100 ml.; total cholesterol, 210 mg. per 100 ml.; cholesterol esters, 175 mg. per 100 ml.; serum sodium, 147 mEq. per liter; serum potassium, 3.9 mEq. per liter. The stool was formed, brown and contained no fat on microscopic examination. Total fat was 24.5 per cent of dry fecal fat, with neutral fat 10 per cent and fatty acids 14.5 per cent.

During the six and a half years of steroid therapy the patient was maintained mainly on oral cortisone; however, in 1950 she received it by the intramuscular route. The injections were discontinued when the patient developed a gluteal abscess and the oral preparation became available. Once in 1950, and at irregular intervals afterward, this medication was interrupted by brief courses of ACTH.

During 1951 and the spring of 1952 the patient's symptoms were well controlled with an average dose of 45 mg. of cortisone daily. In May 1952 a trial with oral hydrocortisone acetate, 100 mg. daily for 20 days, resulted in reappearance of the diarrhea within two weeks and caused a weight loss of eight pounds (from 125 to 117). This was controlled by resuming cortisone in daily doses of 100 mg. for four days. This dose was then gradually reduced to 50 mg. daily. Later in 1952 and during the first two months in 1953 the daily dose of oral cortisone was 25 mg. and the general condition of the patient remained good. In March 1953, during a period of severe illness of one of her children, diarrhea and nausea reappeared and the dosage was raised to 100 mg. daily for three days and then gradually reduced to 75 mg. and then to 50 mg. After two weeks it was possible to return to the previous maintenance dose of 25 mg. of oral cortisone daily. Other compounds proved to be equally satisfactory. Prednisone in oral doses of 10 to 15 mg. per day controlled all the manifestations of the syndrome from May to October 1955. After a brief course of ACTH (20 units of ACTH gel daily for one week), prednisolone in daily oral doses of 10 to 20 mg. was used. The patient believed that her control with this drug was less satisfactory. Therefore cortisone was resumed in March 1956 in somewhat larger doses (75 mg. daily). For the past year the patient has remained on oral cortisone with satisfactory control of most of the manifestations of sprue. She presents, however, two complaints. The first one is referable to vague nervous manifestations (occasional tremor and paresthesias in either hand). The other complaint is of recurring attacks of right upper quadrant pain, at times requiring injections of narcotics. Careful investigation, including roentgen studies of the gastrointestinal tract, the gall bladder and the kidneys, failed to reveal any organic abnormalities that could explain these episodes. With the exception of these two complaints the patient has had a normal life during these six and a half years, working part-time as a medical assistant in addition to her household duties.

This case illustrates the type of patient classified as primary non-tropical sprue resistant to prolonged standard therapy. The administration of cortisone, corticotropin, prednisone and prednisolone over six and a half years resulted in full control of manifestations of the malabsorption syndrome and in the rehabilitation of the patient. It also depicts the various problems encountered during long term management of sprue with steroid therapy.

FATALITIES OBSERVED DURING STEROID THERAPY

Four patients died while receiving steroids. One patient, (Case 29 of table III) responded satisfactorily for two years (15). During the third year of steroid therapy he developed repeated gastrointestinal hemorrhages that persisted after a subtotal gastrectomy. This part of his course and the autopsy findings are described elsewhere (28). There were multiple ulcerations and erosions of duodenum, jejunum and ileum. The jejunum presented a perforated ulcer contiguous with a sub-diaphragmatic abscess. There were also several areas of thickening of the jejunal wall with evidence of jejunitis. It is difficult to evaluate the role of the steroid therapy in the development of these lesions since bleeding and unexplained fever were present before the start of steroids.

The second patient was included in a previous report (Ref. 15, Case 2). A 59-year old Irish woman with sprue symptoms of 15 years' duration, persistent diarrhea and severe hemorrhagic manifestations had three brief courses of therapy with steroids with minimal response. She succumbed to a bilateral pneumonia at another hospital one month after cessation of cortisone therapy. The autopsy findings are reported elsewhere in this symposium (Ref. 29, Case 7).

The third patient, a 66-year old woman, was admitted for the seventh time on December 7, 1951. The diagnosis of sprue was made eight years earlier. The repeated admissions were motivated by either severe diarrhea, hemorrhagic manifestations or symptoms related to hypoalbuminemia or hypocalcemia. She proved refractory to standard therapy that included liver extract, folic acid and vitamin B_{12}. The final admission was for extreme weakness, abdominal pain, anemia, extensive decubitus ulcer and incontinence of feces. She was emaciated and pale. There were skin ecchymoses over arms and thighs. The significant laboratory data were: hemoglobin, 9.1 gm. per 100 ml.; RBC, 3.3 millions per cu. mm.; WBC, 8000 per cu. mm.; platelets, 120,000 per cu. mm.; prothrombin time, 21 seconds (control 12), which increased later to 30 seconds (control 13); serum albumin, 2.18 gm. per 100 ml.; serum globulin, 2.8 gm. per 100 ml.; blood sugar, 60 mg. per 100 ml., with a flat oral dextrose tolerance test; serum vitamin A (fasting), 29 μg. per 100 ml.; carotene, 11 μg. per 100 ml.; fecal fat, 37 to 41 per cent of dry fecal weight. There was radiologic evidence of osteoporosis as well as dilatation and segmentation of the small intestine. The patient was given repeated transfusions and calcium salts to control the tetany.

On December 28, 1951 injections of ACTH were started. The initial daily dose was 80 mg., reduced later to 60 mg. daily. There was a temporary improvement manifested by increase in appetite, sense of well being and subsidence of diarrhea and incontinence. The serum albumin rose to 3.8 gm. per 100 ml. while the serum globulin remained at 2.8 gm. per 100 ml. Fasting serum vitamin A level rose to 82 and serum carotene to 24 μg. per 100 ml. The improvement was transient however. The decubitus ulcer spread rapidly. The prothrombin time rose to 180 seconds. The patient developed uncontrollable tetany and died in coma on February 20, 1952. Autopsy permission was not obtained.

The fourth patient was a 67-year old man, admitted on February 28, 1956 with exacerbation of symptoms of sprue. The diagnosis was established eight years earlier and partial control was achieved with standard diet supplemented at times with liver extract, folic acid and vitamin B_{12}. During the two months prior to admission to the hospital there was an increase in number of stools to five or six daily with a weight loss of 12 pounds, reaching a low weight of 109 pounds. There was marked emaciation and clubbing of the fingers. There was also moderate edema of both ankles. The significant laboratory data were: hemoglobin, 13.9 gm. per 100 ml.; WBC, 8200 per cu. mm.; serum albumin 3.3 gm. per 100 ml.; serum globulin, 2.1 gm. per 100 ml.; glucose, 75 mg. per 100 ml.; fasting vitamin A level, 31 μg. per 100 ml.; carotene, 6 μg. per 100 ml.; fecal fat, 66.4 per cent of dry fecal weight with 40 per cent fatty acids; serum sodium, 142 mEq. per liter; serum potassium, 4.7 mEq. per liter; serum chloride, 107 mEq. per liter; serum calcium, 8.4 mg. per 100 ml.; serum phosphorus, 2.2 mg. per 100 ml. The patient improved on bed rest and a high protein diet supplemented with vitamins. No steroids were deemed necessary. The patient was discharged on March 25, 1955. At home there was a gradual recurrence of diarrhea and progressive weight loss. The number of stools increased to six per day. When he returned to the hospital on August 2, 1955 he appeared markedly cachectic and his weight had decreased to 72 pounds. There was marked clubbing and some edema of the legs. The blood pressure was 80/50. Laboratory findings included: hemoglobin, 11.8 gm. per 100 ml.; white blood cells, 10,000 per cu. mm.; platelets, 102,000 per cu. mm.; prothrombin time, 17 seconds (control 12 seconds); serum sodium, 148 mEq. per liter; serum potassium, 1.8 mEq. per liter; serum chloride, 115 mEq. per liter; serum calcium, 6.8 mg. per 100 ml.; serum phosphorus, 3 mg. per 100 ml. The patient appeared to be moribund. Intravenous ACTH was started together with intravenous administration of serum albumin. Patient expired the next day. Autopsy findings are described elsewhere in this symposium (Ref. 29, Case 10).

PRECAUTIONS IN LONG TERM STEROID THERAPY

It is generally known that the use of these potent hormones is associated with certain hazards such as, thromboembolic phenomena, changes in cardiovascular dynamics, ulcerations with bleeding or perforations of the gastrointestinal tract. In this group of patients complications attributable to steroid therapy have not been frequent. This is probably due to the low doses used during the long term management. Typical moon face or other changes included in the so-called Cushing's syndrome were not observed. Alterations of serum lipids have not been observed. Similarly, only minor cardiovascular changes were observed attributable to salt and water retention.

We have seen, at times, symptoms suggestive of peptic ulcer; but we have never been able to demonstrate a definite peptic ulcer attributable to the prolonged steroid therapy. Systematic administration of antacids in these instances is advisable. An unusual type of ulceration of the small bowel was described above (Case 3, Table III).

Another major problem during long term management with steroids is the possibility of masked infections. We have seen extensive pneumonitis without the usual fever and leukocytosis. Our follow-up routine includes yearly chest films. To date we have not observed reactivation of tuberculosis. Other authors have reported such instances (17). When fractures were observed during steroid therapy it was impossible to determine the part attributable to the basic malabsorption of calcium and vitamin D and the negative balance due to steroid therapy. A detailed discussion of this subject will be found elsewhere in this symposium (25). Similarly the degenerative neurologic manifestations seen in three cases could not be attributed specifically to the steroid therapy (30). There is a report of a psychosis observed in a patient with sprue during administration of large doses of cortisone at the beginning of the treatment, but not with the lower doses used later for maintenance purposes (31).

SUMMARY AND CONCLUSIONS

The management of the malabsorption syndrome has been reviewed. Dietary management, both the so-called conventional diet and gluten-free diet, have been discussed. The milder forms of this syndrome are treated with diet alone or with supplements of liver extract, vitamin B complex, vitamin B_{12}, folic acid and iron. Other vitamins and minerals may be required.

Patients resistant to the above measure can benefit by the use of corticotropin or the cortisones. There is now abundant evidence that prolonged steroid therapy is relatively safe and effective. The possible hazards of this form of therapy must be kept in mind in order to institute preventive and curative measures. Prevention and treatment of complications of steroid therapy have been discussed.

REFERENCES

1. Gee, S.: On the Celiac Affection. St. Barth Hosp. Rep., 24: 17, 1888.
2. Hames, F. M.: Diagnostic Criteria and Resistance to Therapy in the Sprue Syndrome. Am. J. Med. Sci , 204: 436, 1942.

3. Manson-Bahr, P.: The Dysenteric Disorders. II edition. Williams and Wilkins, Baltimore, 1943.
4. Thaysen, T. E. H.: Non-tropical Sprue; A Study in Idiopathic Steatorrhea. Oxford University Press. London, 1922.
5. Haas, S. U., and Haas, M. P.: Diagnostic and Treatment of Celiac Disease. Postgrad. Med., 7: 239, 1950.
6. Van de Kamer, J. M., Weijers, H. A., and Dicke, W. K.: Celiac Disease; Investigation into Injurious Constituents of Wheat in Connection with Their Action on Patients with Celiac Disease. Acta paediat., 42: 223, 1953.
7. Bloomfield, A. L., and Wycoff, H. A.: Remission in Sprue following High Liver Diet. Calif. and West. Med., 27: 659, 1927.
8. Castle, W. B., Rhoads, C. P., Lawson, H. A., and Payne, G. C.: Etiology and Treatment of Sprue. Arch. Int. Med., 56: 627, 1935.
9. Spies, T. D., Milanes, F., Menendez, A., Koch, M. B., and Minnich, V.: Observations on the Treatment of Tropical Sprue with Folic Acid. J. Lab. and Clin. Med., 31: 227, 1946.
10. Juarez, R. M., Juarez, R. M., Jr., Buso, R., and Sabater, J.: The Effect of Orally Administered Folinic Acid in the Treatment of Tropical Sprue. Blood, 9: 489, 1954.
11. Black, D. A. K., and Fourman, L. P. R.: Some Problems of Tropical Sprue. Brit. Med. Jour., 2: 645, 1947.
12. Adlersberg, D., Colcher, H., and Drachman, S. R.: Studies on the Effects of Cortisone and Pituitary Adrenocorticotropic Hormone (ACTH) in the Sprue Syndrome. Gastroenterology, 19: 674, 1951.
13. Almy, T.: A Refractory Case of Idiopathic Steatorrhea (Non-tropical Sprue); with Observations on the Therapeutic Effects of Salt-poor Albumin and Adrenocorticotropic Hormone. Ann. Int. Med., 14: 1041, 1951.
14. Taylor, A. B., Wollager, E. E., Comfort, M. W., and Power, M. H.: The Effect of Cortisone on Non-tropical Sprue (Idiopathic Steatorrhea). Gastroenterology, 20: 203, 1952.
15. Colcher, H., Drachman, S. R., and Adlersberg, D.: Management of Intractable Sprue with Cortisone and Adrenocorticotropin (ACTH). Ann. Int. Med., 38: 554, 1953.
16. Adlersberg, D., Colcher, H., and Wang, C. I.: Oral Use of Hydrocortisone (Compound F) in Treatment of Sprue. Arch. Int. Med., 92: 615, 1953.
17. Lepore, M. in Combined Staff Clinics: Am. J. Med., 15: 790, 1953.
18. Adlersberg, D.: Problems of Management of Idiopathic Sprue. N. Y. State J. Med., 55: 3575, 1955.
19. Adlersberg, D., and Rabinowitz, D.: The Sprue Syndrome: Improved Dietary Management. Am. Dietetic Assoc., 26: 879, 1950.
20. Dickie, W. K.: Celiakie. Thesis. Utrecht, 1950.
21. Anderson, C. M., Frazer, A. C., French, J. M., Gerrard, J. W., Sammons, H. S., and Smellie, J. M.: Celiac Disease: Gastrointestinal Studies and the Effect of Dietary Wheat Flour. Lancet, 1: 836, 1952.
22. McIver, C.: Gluten Free Diet in Idiopathic Steatorrhea: Report of a Case. Lancet, 2: 1112, 1952.
23. Anderson, C. M., Frazer, A. C., French, J. M., Hawkins, C. F., Ross, C. P., Sammons, H. G.: The Influence of Gluten and Antibacterial Agents on Fat Absorption in the Sprue Syndrome. Gastroenterologia, 81: 98, 1954.
24. Ruffin, J. M., Carter, D. D., Johnston, D. H., and Baylin, G. J.: Wheat-Free Diet in the Treatment of Sprue. New Eng. J. Med., 250: 281, 1954.
25. Hartley, J.: Osseous Changes and Fractures in Malabsorption Syndrome. This volume, page 172.
26. Bossak, E. T., Wang, C. I. and Adlersberg, D.: Clinical Aspects of the Malabsorp-

tion Syndrome; Observations in 94 Patients. This volume, page 112.

27. ADLERSBERG, D., MARSHAK, R. H., COLCHER, H., DRACHMAN, S. R., FRIEDMAN, A. I., AND WANG, C. I.: The Roentgenologic Appearance of the Small Intestine in Sprue. Gastroenterology, 26: 548, 1954.
28. HIMES, H. W., GABRIEL, J. S., AND ADLERSBERG, D.: Previously Undescribed Clinical and Postmortem Observations in Non-tropical Sprue: Possible Role of Prolonged Corticosteroid Therapy. Gastroenterology, 32: 60, 1957.
29. HIMES, H. W., AND ADLERSBERG, D.: Pathological Studies in Malabsorption Syndrome. This volume, page 77.
30. SENCER, W.: Neurologic Manifestations in the Malabsorption Syndrome. This volume, page 157.
31. MACKAY, I., AND VOLWILER, W.: The Effect of Cortisone upon Absorption of Protein, Fat and Calcium in Idiopathic Steatorrhea. Gastroenterology, 28: 972, 1955.

MALABSORPTION FOLLOWING EXTENSIVE SMALL INTESTINAL RESECTION INCLUDING INADVERTENT GASTRO-ILEOSTOMY

EDGAR KOGAN, M.D.
ADOLFO SCHAPIRA, M.D.
HENRY D. JANOWITZ, M.D.
AND
DAVID ADLERSBERG, M.D.
New York, N. Y.

Extensive resection of the small intestine may be necessitated by: (a) diffuse inflammatory disease such as tuberculous enteritis or non-specific granulomatous jejuno-ileitis, (b) neoplastic disease of the small bowel, (c) mesenteric venous or arterial thrombosis, or (d) mechanical obstruction of the bowel with compromise of the blood supply as seen in volvulus or intussusception. The outcome following massive resection depends upon a number of factors, the most important of which are the general condition of the patient before resection, the length of remaining intestine and its ability to develop compensatory mechanisms.

The effects of removal of considerable portions of the small gut have been studied in great detail in the experimental animal (1). In most instances the following sequence of events was observed. Initially, steatorrhea and marked loss of weight ensued. Fat and nitrogen losses in the stool often amounted to three-quarters of the intake, whereas carbohydrates were more adequately absorbed. Fat absorption was usually improved by decreasing the amount of fat in the diet. A marked compensatory hypertrophy of the intestinal villi occurred in all animals except those with the most extensive resections and was instrumental in initiating the recovery phase which generally began four to five months after resection. Removal of more than 70 to 80 per cent of the small intestine usually resulted in death due to gradual inanition. In general, 50 per cent removal constituted the upper limit of safety in experimental enterectomy.

We have had the opportunity to observe 11 patients who have had extensive resection of the small bowel; five for jejuno-ileitis and six for acute conditions which caused gangrene of the bowel. Of the latter, resection was performed for mesenteric venous occlusion in two patients and in one patient each for superior mesenteric arterial occlusion, gangrene of the small bowel secondary to herniation of bowel through an incisional hernia, necrosis of ileum and jejunum associated with prolonged Miller-Abbott tube intubation, and volvulus of the small bowel occurring as a post-operative complication of ileo-colectomy for carcinoma of the ascending colon. The last patient succumbed after a seven month post-operative period, the only fatality in the series. The remaining ten cases have been followed for periods ranging from one to twelve years. We are reporting an additional case in which gastro-ileostomy was performed inadvertently in the course of a gastrectomy for duodenal ulcer. Because of the exclusion of a

From the Department of Medicine, The Mount Sinai Hospital, New York, N. Y.

considerable segment of the bowel a nutritional defect resulted simulating the clinical picture observed after massive resection of the gut.

Five case histories have been selected in order to illustrate in detail the problems involved. Three patients had small intestinal resections for jejuno-ileitis and two for acute vascular accidents. These and the remaining cases have been summarized in Tables I through V.

ILLUSTRATIVE CASES

Case 1

S. K., a 43 year old white male, had an appendectomy at the age of 16 years because of intermittent episodes of right lower quadrant pain of three years duration. Several days after the operation, a right lower quadrant fistula developed which drained liquid feces. He was admitted to The Mount Sinai Hospital in 1932 where an ileo-transverse colostomy was performed with exclusion of the fistula which emanated from a granulomatous cecal mass. Six months later, he was readmitted with severe, cramping left lower quadrant pain. At operation, 12 inches of granulomatous terminal ileum were resected. He remained essentially asymptomatic for 20 years.

Early in 1952 abdominal cramps, anorexia, weight loss, mild fever, diarrhea and severe fatigue appeared. Roentgen examination showed extensive disease proximal to the anastomosis. The distal jejunum as well as the remainder of the ileum were involved. In April of that year he was readmitted and at operation the disease was found to be so extensive as to require massive resection of the small and large bowel starting 18 inches below the ligament of Treitz and extending to the distal transverse colon, and jejuno-transverse colostomy. His postoperative course was uneventful except for eight to ten loose stools daily. A low residue diet, deodorized tincture of opium, bismuth subcarbonate, folic acid, vitamins and injections of crude liver extract failed to alleviate the diarrhea. Laboratory studies revealed evidence of malabsorption. An oral glucose tolerance as well as a vitamin A tolerance test showed completely flat curves (Table V). The serum carotene concentration was strikingly low (8 μg. per cent).

In August 1952, he was started on a course of ACTH, 80 units daily by intravenous drip. The improvement was striking. Appetite and strength improved and he gained seven pounds in two weeks. The dosage of ACTH was gradually reduced to 20 units daily and on discharge it was replaced by cortisone, 75 mg. daily, without deleterious effect. In October 1952, while the patient continued with a daily maintenance dose of 25 mg. of cortisone, signs of disordered sensorium appeared and steroids were discontinued in order to prevent a psychosis. His weight, which had fallen some 50 pounds, was now stabilized at 125 pounds. When cortisone was discontinued, he began to note twitching of his facial muscles, tingling sensations and cramps in his legs. He was readmitted to the hospital in November, 1952 for reevaluation of these symptoms. The Chvostek and Trousseau signs were positive. Chemical analyses of blood drawn the day after admission were: serum calcium, 6.4 mg. per cent; phosphorus, 2.8 mg. per cent; alkaline phosphatase, 9 King Armstrong units; total protein, 6.4 mg. per cent; albumin 2.5 and globulin 3.9 gm. per cent; and total cholesterol, 120 mg. per cent. The esterified cholesterol was 75 per cent of the total. The fecal fat amounted to 55.8 per cent of the dry stool weight, 41.7 per cent comprising the fatty acid portion. Vitamin A tolerance test revealed improved absorption of fat-soluble vitamins although the level of carotene in the serum was still extremely low. Glucose tolerance test showed somewhat improved absorption, although the curve was not completely normal. Gastric analysis after administration of histamine showed absence of hydrochloric acid. Urinalysis was positive for albumin. There was fixation of the specific gravity at 1.010 and reduction in the excretion of phenolsulphthalein to 42 per cent. Electrolyte and renal clearance studies were interpreted as compatible with the diagnosis of renal tubular acidosis. This was perhaps related to repeated episodes of dehydration, loss of potassium and subsequent renal ischemia producing chronic renal insufficiency.

Roentgen examination revealed normal residual small bowel; barium was seen in the colon after 15 minutes. There was a moderate degree of demineralization of the bones.

Several days after admission, he had a tetanic convulsion which responded to intravenous calcium gluconate. He was placed on high doses of calcium lactate and vitamin D by mouth. This resulted in a complete cessation of muscular twitching. Although diarrhea persisted (average of seven evacuations daily) he was discharged markedly improved on a high calorie, high protein, high carbohydrate, low residue diet with liberal amounts of salt and potassium chloride. Vitamin D and calcium lactate were continued in high doses.

He remained well until August 1953 when a non-specific febrile illness again precipitated acidosis, cramps, vomiting, dehydration and postural hypotension. Chemical analysis revealed severe electrolyte imbalance as evidenced by: the CO_2 combining power of 13.6 vol. per cent and the sodium 125 mEq./L. After therapy with parenteral fluids and electrolytes, he became afebrile, the abdominal cramps subsided and his appetite improved. Repeated serum electrolyte studies showed the CO_2 combining power to be 69 vol. per cent, and the sodium to be 144 mEq./L., and the chloride to be 114 mEq./L. The diarrhea persisted with six to ten stools daily. Small bowel study again revealed a normal jejunum. Thirty minutes after ingestion of barium, the head of the column was seen in the rectum.

The patient's condition remained good until January 1954, when he was admitted because of rectal bleeding thought to be caused by recurrent jejunitis. X-ray examination failed to confirm this assumption. After control of the bleeding by conservative measures, he remained well until the latter part of 1954 when rectal bleeding recurred. The hemoglobin on admission was 6.8 gm. per cent, the prothrombin time was 18.5 sec. (control 11 sec.), serum albumin was 2.0 gm. per cent, and serum globulin was 3.3 gm. per cent. The bleeding promptly ceased after administration of vitamin K and the prothrombin time returned to normal. He was given fluids, electrolytes, one blood transfusion, and then oral iron therapy was begun. Anoscopic examination revealed an anal fissure posteriorly and external hemorrhoids. He later developed a perirectal abscess which required incision and drainage.

In 1955, he remained comparatively well. There were intermittent episodes of mild abdominal cramps and four to seven soft but formed bowel movements per day. Careful selection of diet and multivitamin preparations constituted his therapy. Calcium salts and all forms of iron produced severe abdominal cramps and were withheld. During a two month period of steroid therapy (10 mg. of hydrocortisone by mouth daily) he gained ten pounds but once again, the development of mental confusion required the discontinuance of this medication. In January, 1956 he was hospitalized for progressive swelling of the buttocks and pruritus. On physical examination, he showed areas of excoriation especially marked over the buttocks with the skin over the perineum showing a red macular eruption. There was an abscess present between the fourth and fifth toes of the right foot.

Urine analysis revealed 1+ albumin, but was otherwise negative. Hemoglobin was 8.7 gm. per cent. The red cells were hypochromic. Abnormal blood findings included: serum alkaline phosphatase, 19 King Armstrong units; total protein, 5.7 gm. per cent, albumin, 2.0 and globulin, 3.7 gm. per cent. Oral glucose tolerance test revealed a flat curve. A vitamin A tolerance test showed a low fasting level and delayed absorption. The serum carotene level was extremely low (3 μg. per cent).

The secretin test (performed by Dr. David Dreiling) revealed normal volume with low bicarbonate concentration and low concentration of amylase, indicating pancreatic insufficiency as seen in pancreatic fibrosis (see Table IV). Gastric analysis revealed a histamine-resistant achlorhydria. The stools contained large amounts of fatty acids and considerable neutral fat. The Schilling test demonstrated complete lack of vitamin B_{12} absorption. Roentgen studies of the remaining small bowel were again negative.

He was treated with salt-free albumin and blood, which raised his serum albumin level to 3.3 gm. per cent. The abscess healed readily with the use of antibiotics. He was given 9 grams of pancreatin daily but this proved ineffective in controlling the diarrhea and steatorrhea. Because of previous episodes of mental confusion during treatment with the steroid hormones there was some hesitancy to administer these agents. A cautious trial with prednisone had very gratifying results, and he has been maintained on 20 mg. of prednisone daily to the time of this writing (Oct. 1956). His weight is now 140 pounds, appetite is satisfactory and the pruritus is under control. He has five formed stools daily. His diet consists of 350 grams of carbohydrate, 100 grams of protein and 60 grams of fat. In addition to prednisone and a weekly injection of corticotropin, he also receives potassium chloride, vitamin D, calcium lactate and testosterone.

The most recent roentgen study of the gastrointestinal tract revealed the jejunum to be longer than 18 inches, perhaps a compensatory hypertrophy.

It is of interest that among the close blood relatives of this patient there is a high incidence of jejuno-ileitis and colitis (Fig. 1).

Comment. This patient's symptoms began in 1929 at the age of 13 years. Three years later an appendectomy was performed for "chronic appendicitis". Because of a fistulous tract extending to and from a mass in the pericecal region an ileotransverse colostomy with exclusion of the mass was performed several months later. After resection of one foot of granulomatous ileum in 1932 a remission of almost 20 years resulted. In 1952 when disease recurred, all of the involved small bowel was eradicated by extensive resection and only 18 inches of proximal jejunum were left. The postoperative course was complicated by almost continuous diarrhea, vomiting, anorexia, intercurrent infections, dehydration, cachexia, tetany, and renal involvement which suggested tubular acidosis. There was severe impairment of intestinal absorption in the immediate postoperative period, with flat glucose tolerance and flat vitamin A tolerance curves. Six months later there was improvement in the absorptive capacity of the bowel

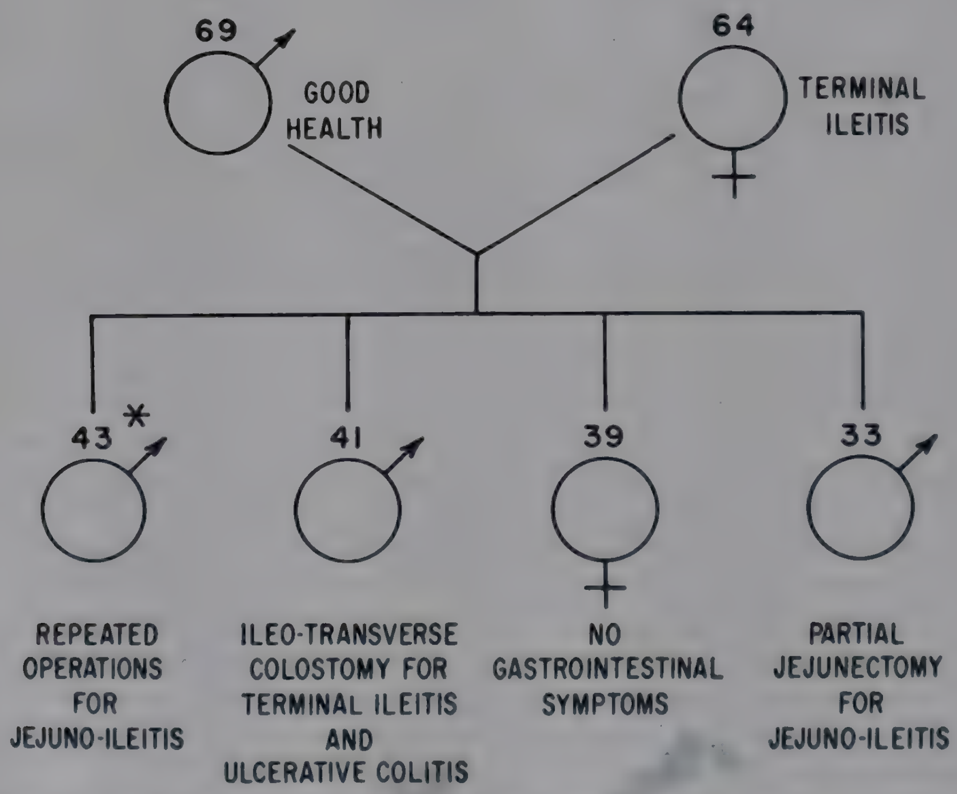

69
GOOD HEALTH
64
TERMINAL ILEITIS
43
*
41
39
33
REPEATED OPERATIONS FOR JEJUNO-ILEITIS
ILEO-TRANSVERSE COLOSTOMY FOR TERMINAL ILEITIS AND ULCERATIVE COLITIS
NO GASTROINTESTINAL SYMPTOMS
PARTIAL JEJUNECTOMY FOR JEJUNO-ILEITIS

FIG. 1. Family tree of patient 1. Asterisk indicates the index patient (proband). His mother and one brother had jejuno-ileitis; another brother had terminal ileitis and ulcerative colitis; a sister had no gastrointestinal disease.

It is noteworthy that the patient received steroid therapy during this six month interval. Bleeding episodes in 1954 may have been due to hypoprothrombinemia and inflammation at the anastomotic site, but there was no evidence that disease had recurred in the remaining jejunum. Recently, treatment with prednisone and ACTH has resulted in marked improvement in his general condition.

Case 2

D. H. is a 58 year old white female who, because of abdominal pain, had an exploratory laparotomy performed in 1945 at another hospital. The diagnosis of jejuno-ileitis was established but no definitive procedure was done because the disease was considered too diffuse. In May 1950 severe abdominal pain recurred and she lost considerable weight. Two months later, during her first admission to The Mount Sinai Hospital (July 1950), it was decided to treat the disease surgically. At operation all of the small bowel except for six feet of proximal jejunum was found involved in the disease process. A jejuno-transverse colostomy was constructed about five feet from the ligament of Treitz, by-passing all of the diseased bowel. The postoperative course was uneventful except for four semi-formed bowel movements per day. Her condition continued to improve over a six month period but in December 1950 she again began to lose weight and had recurrent abdominal cramps. She was readmitted to the hospital where the short-circuited intestine together with the cecum was resected and a new jejuno-transverse colostomy performed. She was left with approximately three feet of small bowel. In the first six months after operation, she had two to four semi-formed evacuations daily and her condition improved markedly.

In May 1951 the patient began to have four to five diarrheal stools daily, following the ingestion of foods or liquids. She restricted her diet and soon showed evidences of malnutrition and dehydration. When readmitted to the hospital, she was given frequent feedings, a diet high in vitamins, tincture of opium, Kaopectate and sedation. The diarrhea subsided and she gained six pounds in one week. Shortly after discharge she again developed diarrhea. Examination of the stool revealed a large amount of fatty acids and neutral fats. On the assumption that increasing the length of functioning colon would increase the absorption of water and solidify the stools, it was decided to convert the jejuno-transverse colostomy to a jejuno-ascending colostomy, thus adding 12 inches to the functioning colon. The results were indeed gratifying, as the diarrhea subsided after operation. She was well until November 1952 when anemia was noted for the first time, and she was hospitalized for investigation of this problem. Hematologic studies revealed the following: hemoglobin, 6.6 gm. per cent; red blood count, 2.9 million per cu. mm.; hematocrit, 29 per cent; white blood count and differential counts were normal. The blood smear showed an absence of macrocytes; the red cells, generally well filled with hemoglobin, were small and uniform in size and shape. A bone marrow puncture showed mild granulocytic hyperplasia, but was not diagnostic. Serum iron was 51 μg. per cent and total iron binding capacity 363 μg. per cent. The platelets were adequate in number and morphologically normal. The Coombs' test was negative as were the stool guaiac examinations. The anemia was thought to be due to poor iron absorption. After six blood transfusions her hemoglobin was 13.8 gm. per cent. She was discharged on a high calorie, low residue diet with supplemental feedings, multivitamins, ferrous sulfate and sedation.

In April, 1953 she complained of rectal discomfort. Examination revealed extensive internal and external hemorrhoids for which hemorrhoidectomy was performed uneventfully. In May, 1953 the patient fell on her right side. This resulted in severe pain in the region of the right hip with loss of function of that joint. Roentgen examination revealed a chip fracture and also marked osteoporosis of the skeletal system. Pain and disability persisted for many months until traction was applied.

In December 1953, the patient was hospitalized because of severe posterior neck pain which had existed for several months. Roentgen studies showed narrowing of the interspaces between cervical vertebrae 4–5 and 5–6. Treatment with hormones was instituted for osteoporosis. In 1954 she was comparatively well, although recurrent anemia necessitated transfusions and admission to the hospital on several occasions. In January 1955, she was hospitalized because of weakness and recurrence of diarrhea. The abdomen was soft and a non-tender liver was palpated one and a half fingers beneath the costal margin. The hemoglobin was 10.2 gm. per cent. The red blood count was 3.85 million per cu. mm. The reticulocyte count was 3.8 per cent. Chemical analyses of the blood revealed the following: serum bilirubin, 0.17 mg. per cent; alkaline phosphatase, 16.7 King Armstrong units; total protein, 6.2 gm. per cent with albumin 2.9 and globulin 3.3 gm. per cent. The calcium level was 7.5 mg. per cent and the phosphorus, 2.5 mg. per cent. Barium meal examination showed the stomach, duodenum and residual jejunum to be normal. The transit time was rapid; the cecum filled with barium in 30 minutes. The skeletal system showed marked generalized demineralization. The patient was treated with Kaopectate and deodorized tincture of opium and the diarrhea rapidly subsided. She was discharged on high doses of calcium lactate, calciferol and testosterone.

In August 1955 she was admitted because of crampy right lower quadrant pain and diarrhea. Physical examination revealed a dry and fissured tongue. The abdomen was slightly distended and active bowel sounds were present. The liver was enlarged two fingers below the costal margin and was non-tender. No other organs or masses were palpable. Liver function tests were negative. Recurrent disease of the small bowel was suspected, but x-ray study did not confirm this impression. The diarrhea was controlled with the usual anti-diarrheal agents and the general condition rapidly improved. She was discharged on a high protein diet, vitamin B_{12}, testosterone, ferrous sulfate and multivitamins.

Recurrent severe anemia has necessitated readmission to the hospital on three occasions for which she received multiple blood transfusions. When last seen (September 1956), she weighted 92 pounds, 12 pounds more than her preoperative weight, her appetite was good and she was having three or four semi-formed bowel movements daily. Therapy included oral ferrous sulfate, calcium lactate, testosterone and vitamin B_{12}.

Comment: The diagnosis of jejuno-ileitis was established in 1945. Five years later a jejuno-transverse colostomy was done excluding all but six feet of proximal jejunum. She remained well for six months but then symptoms recurred, requiring resection of the by-passed intestine and cecum and establishment of a jejuno-transverse colostomy. Approximately three feet of proximal jejunum were left behind. Six months after resection, because of diarrhea and inability to gain weight, the jejuno-transverse colostomy was converted into a jejuno-ascending colostomy in order to increase the length of functioning colon, perhaps thereby increasing the absorption of water and electrolytes. The operation was helpful; her stools became solidified and she gained weight. Her chief remaining problem has been severe anemia, probably due to poor iron absorption which has required frequent transfusions. An additional difficulty has been osteomalacia, manifested by pseudo-fractures, collapsed vertebrae and diffuse demineralization of the entire skeletal system. Although she weighs only 92 pounds, this is 12 pounds more than her preoperative weight. She is not troubled by diarrhea, having three or four semi-formed bowel movements per day.

Case 3

I. R., A 30 year old white male, was admitted to The Mount Sinai Hospital in September 1955, complaining of diarrhea of four weeks duration. His illness began in 1945 with episodes of severe crampy abdominal pain usually associated with vomiting. In 1947 diarrhea was accompanied by abdominal cramps and he suffered a 20 pound weight loss. From 1945 to 1949 he had four upper gastrointestinal roentgen examinations and two barium enema studies with no abnormalities noted. In February 1949, a small bowel study revealed a markedly dilated loop of jejunum and he was hospitalized in March 1949, with the diagnosis of regional enteritis. Laboratory data showed a hemoglobin of 13.2 gm. per cent and a serum albumin concentration of 4.2 gm. per cent and globulin of 3.4 gm. per cent.

Exploratory laparotomy in March 1949 revealed seven areas of segmental enteritis involving the proximal jejunum, starting about 20 cm. distal to the ligament of Treitz and extending over seven feet of jejunum with skip areas of normal jejunum between the lesions. The mesentery of the involved jejunum was markedly edematous and thickened with enlarged lymph nodes. Large inflammatory nodes were present over the pancreas. The remainder of the gastrointestinal tract appeared normal. The bowel proximal to the involved jejunum was dilated and hypertrophied to a moderate degree. Since the involvement was localized to seven feet of bowel, a resection of the involved bowel with a side-to-side anastomosis was performed.

Following operation, the patient showed marked improvement and gained 60 pounds in six months. He remained well for a period of three years when he again developed voluminous diarrhea of foul smelling stools. Abdominal cramps occurred much more frequently than they did prior to resection. In 1951 treatment with broad spectrum antibiotics was ineffectual. In 1952 cortisone therapy resulted in no improvement. In 1953 and again in February 1955 he had episodes of tarry stools and required blood transfusions. Laboratory data prior to transfusions in March 1953 revealed a hemoglobin of 4.3 gm. per cent; RBC, 1.7 million per cu. mm., serum calcium, 8.2 mg. per cent, albumin, 2.2 gm. per cent and globulin, 1.7 gm. per cent. His disease was marked by periods of remissions and exacerbations. He had frequent attacks of paresthesias followed by carpal spasms suggestive of tetany. He noted bright red blood in the stools and edema of the ankles following very severe bouts of diarrhea.

In August 1955 he had a recurrence of diarrhea, mild abdominal cramps and weakness. Four weeks of bed rest, low residue diet and anti-diarrheal agents failed to check the symptoms and he was admitted to the hospital September 1955.

Physical examination revealed an emaciated young man, chronically ill, weighing 109 pounds. Temperature was 101°F., pulse rate 116 per minute, blood pressure 115/60. He was moderately dehydrated and severely anemic. The abdomen was moderately distended. No viscera or masses were palpable. Rectal examination was negative except for hemorrhoids. The stool was tan, liquid and guaiac-positive. Lymph nodes were present bilaterally in the inguinal region and in the right axilla. The Chvostek and Trousseau signs were positive.

Laboratory data: Hemoglobin, 6.1 gm. per cent; WBC, 5000 per cu. mm., with a normal differential count; ESR, 61 mm. (Westergren). Chemical analysis of the serum: blood urea nitrogen, 10 mg. per cent; fasting blood sugar, 97 mg. per cent; albumin, 2.8 and globulin, 2.2 gm. per cent; calcium, 8.2 mg. per cent; phosphorus, 3.2 mg. per cent; alkaline phosphatase, 9.0 King Armstrong units; serum iron, 33 μg. per cent; total iron binding capacity, 250 μg. per cent. Oral glucose and vitamin A tolerance tests were flat and the secretin test of pancreatic function was abnormal. The fat content of the feces was 56.4 per cent of the dry fecal weight, fatty acids accounting for 20.8 per cent of the total.

Barium enema examination revealed marked dilatation and redundancy of the colon. There was no delay or obstruction to the retrograde flow of barium. An upper gastrointestinal and small bowel examination was reported as follows: There were no abnormalities in the stomach or duodenum. Some of the barium left the stomach promptly and visualized the proximal loops of jejunum. The mucosal pattern of the most distal portion of the duodenum and the adjacent portion of the jejunum was thickened and somewhat irregular but this region appeared to be normally distensible. However, beginning four or five inches from the ligament of Treitz the outlined loops of jejunum were markedly irregular in configuration, contained secretions, and the mucosal pattern was markedly effaced. In this region there appeared to be an area of saccular dilatation about 2½ inches in diameter which retained barium. Loops of jejunum distal to this saccular dilatation occupied the left side of the abdomen and the left iliac fossa and showed a marked irregularity and coarse nodular thickening of the mucosal pattern. These loops never filled well with barium nor were any loops distal to these on the right side of the abdomen well visualized at any time. Barium was seen in the ascending colon about three hours after the administration of barium by mouth, but the region of the ileocecal valve could not be identified. The colon was markedly distended with air throughout its course. About ten hours after the administration of barium the dilated saccular structure described above was located in the mid-line and a small amount of barium was seen in the descending colon and sigmoid. Twenty-four hours after the administration of barium, there was no evidence of retention in the saccular structure. A loop of bowel on the right side of the pelvis was seen at this time and also showed a markedly nodular irregular mucosal pattern. This did not appear to be dilated. The findings described were indicative of inflammatory disease of practically all of the small bowel. The most severe disease appeared to be a short distance from the ligament of Treitz on the left side of the abdomen. There was a strong possibility that multiple fistulas existed in this area.

The patient was treated with intravenous serum albumin, parenteral calcium gluconate, multivitamins, Kaopectate and sedation, in addition to receiving three blood transfusions which brought his hemoglobin up to 11.4 gm. per cent. After ten days his condition was only slightly improved and therapy with ACTH, 40 units daily intramuscularly, was started. Four days later, he had a massive rectal hemorrhage requiring five blood transfusions. The corticotropin therapy was discontinued but he had three more massive rectal hemorrhages during the next seven days. Each episode was accompanied by colicky abdominal pain requiring parenteral codeine. Numerous transfusions were required to replace the blood loss. Conservative therapy was continued and one week after the fourth hemorrhage the stools were negative for occult blood. After the bleeding ceased, his appetite improved and he gained six pounds in two weeks. His strength increased and his general condition improved sufficiently to warrant discharge to a convalescent home 12 days after his stool contained no occult blood.

Comment: This patient's disease was originally confined to seven feet of proximal jejunum, and the improvement in his condition after resection of the diseased tissue was indeed dramatic. Three years after operation, he had a recurrence of jejunitis which soon developed into jejuno-ileitis and resulted in a 65 pound weight loss. X-rays four years after recurrence, showed diffuse involvement of the entire remaining small bowel with multiple fistulas present. Profound disturbances in intestinal absorption resulted, as evidenced by tetany, edema, flat glucose and vitamin A tolerance tests, abnormal secretin test, and a high percentage of fat in the stools. An additional complication was recurrent massive hemorrhage from the bowel, not commonly seen in jejuno-ileitis, which was a distinct threat to the life of this patient.

Resection of seven feet of small intestine is considered "massive", but resection of this magnitude is not necessarily accompanied by serious sequelae. However, when the balance of the small intestine became involved in the inflammatory process, the full-blown malabsorption syndrome ensued.

Case 6

E. G. was a 53 year old female who in 1938 had a combined abdomino-perineal resection for carcinoma of the rectum with a permanent sigmoid colostomy. In 1947, a laparotomy was performed because of the sudden onset of bloody diarrhea. There was no evidence of recurrence of the malignancy and the etiology of the acute diarrhea was not determined. In August 1948, she was admitted to the Syracuse University Hospital in profound shock. Laparotomy revealed gangrenous bowel in a large ventral hernial sac at the site of the previous laparotomy. Torsion of the mesentery had occurred and the entire small intestine was gangrenous from a point 18 inches distal to the ligament of Treitz to the cecum. Seven feet of small intestine were resected. The patient survived the procedure but developed constant severe diarrhea from the colostomy. Drugs to thicken the stool, including deodorized tincture of opium, paregoric, bismuth and atropine were unsuccessful in controlling the diarrhea. When she began oral feedings, they were provided as easily assimilated foods such as glucose and protein hydrolysates fortified with vitamins in adequate doses. She tolerated small volumes of foods at frequent intervals, but large meals caused dyspepsia. After returning home, she averaged six to eight small feedings a day with supplements of glucose, milk, proteins, vitamins and calcium. Fats were poorly tolerated and were reduced to a minimum. She consumed 2000 to 2500 calories a day. A gastrointestinal series performed several months after discharge revealed a very small residual segment of small intestine, 18 inches in length, with only moderate dilatation of this loop. Sharp weight loss and progressive cachexia were anticipated but the patient did not deteriorate seriously. Her weight slowly fell from the preoperative level of 120 pounds to 100 pounds. The chief cause of her disability rested with the almost continuous discharge from the colostomy. The skin and muscle turgor remained good, and she never demonstrated evidences of gross vitamin deficiency. Blood studies at monthly intervals showed normal blood counts and blood protein levels. Although she was unable to do a full day's work, she was capable of light household duties.

In an effort to explain the maintenance of an adequate nutritional state in the face of gross intestinal deficiency, the patient was admitted to University Hospital in Syracuse, New York in January 1949, where special studies on absorption and excretion of nitrogen and fat were done (2). They demonstrated that the patient was unable to absorb much fat, but partition studies showed that fat hydrolysis was carried on in normal fashion. Fats in the stools amounted to 42.8 per cent of the dry weight while the fatty acid fraction was 31.2 per cent. Soaps and neutral fats were excreted in normal quantities. Nitrogen balance studies indicated that she absorbed only slightly more than half of the nitrogen ingested, but this was enough to maintain a positive balance. An oral glucose tolerance test was normal.

In March 1950, she was admitted to The Mount Sinai Hospital for further metabolic studies and treatment of the diarrhea. Physical examination revealed a poorly nourished female weighing 85 pounds. The positive physical findings were limited to the following: the tongue was smooth, somewhat shiny and red; a patent colostomy was seen with no induration or skin irritation in the region of the stoma; 2 plus pitting ankle edema, and clubbing of the fingers.

Hematologic determinations and chemical analysis of the serum was within normal limits except for a slight elevation in the alkaline phosphatase. Oral glucose and vitamin A tolerance tests were normal, although the fasting level of vitamin A in the serum was low. The serum carotene concentration was very low. Two days later Tween 80 was added to the oily suspension of vitamin A. The test was repeated and showed some improvement of vitamin A absorption (Table V).

She was placed on a high protein diet with frequent feedings of bananas and strawberries between meals. She was given 15 μg. of vitamin B_{12} parenterally for one week, along with deodorized tincture of opium. These measures did not control the diarrhea. She was then given calcium carbonate to decrease the acidity of the intestinal contents because of the possibility that the low pH of the intestinal contents might have been a factor in producing the hypermotility. Coincident with the administration of calcium carbonate, the patient's stools became formed. She gained five pounds, and her general well being improved remarkably. Roentgen studies with the administration of calcium carbonate showed a distinct decrease in the passage time through the small intestine. When a barium meal was given without the calcium, the small bowel was visualized for one hour and barium appeared at the colostomy site at the end of this time. Several days later when calcium carbonate was administered with the barium meal, the small bowel remained visualized for over three hours and barium did not appear at the colostomy site until three and one-half hours after the meal. One week prior to discharge the opium was discontinued and only calcium carbonate was administered. The diarrhea recurred indicating the need for both the deodorized tincture of opium and the calcium carbonate. She was discharged on these agents in addition to a low residue, high carbohydrate, high protein, low fat diet, with vitamin supplement.

After her return to Syracuse, she was seen at frequent intervals by Drs. Berman and Haft for one year but then was lost to follow-up. During that year she was able to indulge in non-strenous activities. She suffered frequent bouts of diarrhea but maintained her weight between 90 and 95 pounds.

Comment. Nine years after an abdomino-perineal resection for carcinoma of the rectum, which resulted in a permanent sigmoid colostomy, this patient had seven feet of gangrenous small bowel resected because of ventral herniation of the bowel through an incisional hernia. She recovered from the operation which left her with only 18 inches of proximal small bowel. Her nutritional status remained remarkably good despite voluminous discharges from her colostomy. Studies indicated good carbohydrate absorption, positive nitrogen balance, but excessive fat loss in the stools. Study of lipid absorption by the vitamin A test three months later indicated improved fat absorption. The ability of the intestine to absorb glucose and protein improved more readily than fat. The improvement in fat absorption noted so soon after resection was a good prognostic sign.

Case 7

A. S., a 66 year old white female, was admitted to The Mount Sinai Hospital in November 1954, for treatment of long standing hyperthyroidism. Administration of radioactive iodine was successful in amelioration of the symptoms except for chronic auricular fibrillation which persisted.

In May 1955, she was readmitted for conversion of arrhythmia. She was treated with digitalis and then with quinidine, with conversion to regular sinus rhythm. She was discharged in good condition. As she was leaving the hospital, she developed severe abdominal pain and was readmitted. Emergency surgery was deemed necessary. Exploratory laparotomy revealed extensive small bowel infarction secondary to embolization of the superior mesenteric artery. The small bowel, except for 18 inches of jejunum, was resected as well as the right side of the colon and the proximal half of the transverse colon. The postoperative course was complicated by acute cholecystitis with jaundice requiring cholecystectomy on the eighth postoperative day. Following the bowel surgery, she had five to ten diarrheal stools per day and her weight decreased from 119 to 96 pounds. She stabilized sufficiently on vitamins and Kaopectate to allow discharge.

She was readmitted in August 1955 because of recurrence of diarrhea and muscular twitchings suggestive of hypocalcemia. Malabsorption was evident on this admission. Laboratory studies revealed the following: hemoglobin, 10 gm. per cent, calcium, 7.8 mg. per cent; total protein, 7.4 gm. per cent; albumin, 3 gm. per cent; and globulin, 4.4 gm. per cent. The prothrombin time was 14.5 seconds (control, 12 seconds). An oral glucose tolerance test and a vitamin A tolerance test showed markedly impaired absorption of carbohydrate and fat and there was no absorption of vitamin B_{12} as measured by the Schilling test. Roentgen examination of the residual small bowel and colon was negative except for rapid transit time; barium appeared in the colon in 15 minutes. Stool examinations were negative for occult blood and neutral fat, but fatty acids were present in abundance. Gastric analysis showed normal acidity.

The diarrhea persisted despite Kaopectate, deodorized tincture of opium, calcium chloride and a high calorie, low fat diet. It was not until cortisone, 100 mg. daily, was added to the regimen that her condition improved. She gained five pounds in two weeks and her evacuations were limited to two semi-formed stools per day. She was discharged in October 1955 on prednisone, 30 mg. per day. Supportive therapy included vitamins and Kaopectate.

When last seen in March 1956, her general condition was good, although she weighed only 102 pounds. She had three to four bowel movements per day which were semi-formed, yellowish and occasionally fatty. Hematologic and serum chemistry studies were normal.

Comment. The sequence of events that created this patient's nutritional problem is of interest. In 1955, she was hospitalized for conversion of chronic auricular fibrillation. This was easily accomplished with digitalis and quinidine. She was discharged the day after conversion and as she was leaving the hospital developed acute abdominal pain. Exploratory laparotomy revealed extensive small bowel infarction secondary to an embolus from the superior mesenteric artery. After an extensive resection, she was left with approximately 18 inches of jejunum. The postoperative course was complicated by jaundice requiring cholecystectomy on the eighth day. Since then, the patient has been troubled with weight loss, diarrhea, abdominal cramping pain, tremulousness and irritability. Extensive workup three months after operation revealed flat vitamin A and glucose tolerance curves, failure to absorb vitamin B_{12}, rapid intestinal transit time and moderate demineralization of the bones. The diarrhea was not controlled by the usual agents and her weight dropped from 98 to 84 pounds. Upon the administration of cortisone, the diarrhea rapidly abated, and she gained seven pounds in two weeks. She has been maintained on prednisone and has been doing remarkably well although confined to her home for the most part.

Case 12

L. S., a 64-year old male, was admitted to The Mount Sinai Hospital in January 1956 complaining of weakness and weight loss following subtotal gastrectomy.

The patient had no gastrointestinal complaints until two years prior to admission when he developed abdominal pains which occurred two hours after meals. A roentgen study of the upper gastrointestinal tract at that time was reported as negative. In July 1955 he had an episode of hematemesis while in Florida. He was treated with transfusions until bleeding ceased and then discharged without investigation of the source of bleeding. Upon arrival in New York City he had a recurrence of hematemesis and was hospitalized at another institution. He received eight units of blood in two days but the bleeding persisted and on the third hospital day, a subtotal gastrectomy for duodenal ulcer was performed. He was discharged on the twelfth postoperative day on a diet of milk, cereal and baby food which was gradually increased, but the patient failed to gain weight although his appetite was excellent and he was consuming three large meals daily supplemented with vitamins and iron. His weight gradually fell from the preoperative weight of 148 pounds to 108 pounds. In October 1955 he had an episode of dizziness followed by the passage of tarry stools and subsequent fainting and was readmitted to that hospital. After the bleeding was controlled, a vagotomy was suggested but refused by the patient. Shortly after discharge he noted a change in bowel habits, his movements became more frequent and soft. Because of persistent weakness and inability to gain weight he was admitted to The Mount Sinai Hospital for investigation.

Physical examination was negative except for evidence of marked weight loss. Laboratory data: hemoglobin, 10.5 gm. per cent; WBC, 6,000 with a normal differential count; erythrocyte sedimentation rate, 5 mm. per hour (Westergren method); blood urea nitrogen, 18 mg. per cent; fasting blood sugar, 83 mg. per cent; total protein, 5.0 gm. per cent; albumin, 2.6 and globulin, 2.4 gm. per cent; bromsulfalein (5 mg., 45 min. test), 1.8 per cent retention of the dye; alkaline phosphatase, 17.1 King Armstrong units; acid phosphatase, 3.8 King Armstrong units; prothrombin time, 15 seconds (control—12 seconds); cephalin flocculation, 2 plus. On gastric analysis the free hydrochloric acid was 22 mEq. per liter. Total acidity was 36 mEq. per liter. Examination of the feces for neutral fat and fatty acids was negative, as was the guaiac test for occult blood. An oral glucose tolerance test (100 gm. glucose) showed 83, 88, 97, 101 and 85 mg. per cent after 0, 30, 60, 120 and 180 minutes respectively. It was interpreted as a flat curve. A vitamin A tolerance test (180,000 u. vitamin A in oil) revealed the following vitamin A serum levels: fasting 26; after 4 hours, 44; 6 hours, 42; and 8 hours, 36 μg. per cent. Serum carotene concentration was 18 μg. per cent. Thus, the tests of intestinal absorption showed marked impairment of the absorptive capacity of the small bowel. A gastrointestinal series revealed that the site of the previous anastomosis was only two feet from the ileocecal valve. The stomach had been inadvertently anastomosed to the ileum.

The cause of the malabsorption was now established and the patient was again operated upon. The original anastomosis was found to be a gastroileostomy. This was resected and a gastrojejunostomy established. The postoperative course was uneventful. Within a week he was eating soft foods without difficulty and had started to gain weight. He was discharged on the eleventh postoperative day in good condition. When he was last seen, eight months after discharge, he was asymptomatic and weighed 145 pounds, only three pounds below his normal weight. The total weight gain after the operation amounted to 37 pounds.

Comment. Failure to gain weight following subtotal gastrectomy for duodenal ulcer performed six months prior to admission was the chief complaint of this patient. There was evidence of malabsorption as indicated by the glucose tolerance and vitamin A tolerance tests. Roentgen study revealed the underlying defect for the barium, administered by mouth, flowed directly from the stomach to the distal ileum. The surgical error was rectified, the postoperative course was uneventful and the patient gained 37 pounds in weight. The decisive factor causing malabsorption and the weight loss was the exclusion of all but a small segment of small bowel. The resulting malabsorption syndrome simulated massive resection of the small intestine.

CLINICAL FEATURES

Table I summarizes the clinical features of the patients. The group with jejuno-ileitis included three men and two women whose ages at the time of resection ranged from 18 to 52 years (average 38). Patient 1 had a most extensive resection; only one and one-half feet of small bowel remaining. As anticipated, this patient had an extremely stormy course after operation as did patient 2 who had all but three feet of jejunum resected. Patient 3 had six feet of jejunum resected and had a smooth postoperative course. He remained in good health for three years when disease recurred affecting almost all of the remaining small intestine. This resulted in severe impairment of absorption similar to that seen after a 90 per cent resection. Cases 4 and 5 had 50 per cent or less of the small bowel resected with no significant weight loss or nutritional deficiency. Case 6 through 11 were patients who had extensive resections for acute vascular emergencies which compromised the blood supply to the bowel. This group consisted of four females and two males ranging in age from 21 to 68 years (average 51).

TABLE I

Clinical features

Case No.	Age at Resection	Sex	Disease	Magnitude of Resection or Length of Remaining Small Intestine	Period of Observation
1. S. K.	39	M	Jejuno-ileitis	1½ ft. proximal jejunum remaining	3½ yrs.
2. D. H.	52	F	Jejuno-ileitis	2½ ft. proximal jejunum remaining	7 yrs.
3. L. R.	24	M	Jejuno-ileitis	7 ft. proximal jejunum resected	7 yrs.
4. S. R.	41	F	Jejuno-ileitis	50% of small bowel resected	11½ yrs.
5. P. G.	18	M	Jejuno-ileitis	5 ft. jejunum resected	2 yrs.
6. E. G.	53	F	Herniation of bowel through hernial sac—gangrene of 17 ft. of small intestine	1½ ft. jejunum remaining	2 yrs.
7. A. S.	64	F	Superior mesenteric arterial occlusion	1½ ft. jejunum remaining	2 yrs.
8. M. S.	64	M	Necrosis of jejunum and ileum caused by indwelling Miller-Abbot tube	3 ft. jejunum remaining	8½ yrs.
9. W. B.	37	M	Mesenteric venous thrombosis	7 ft. jejunum remaining	9 yrs.
10. S. M.	21	F	Mesenteric venous thrombosis	5 ft. of small bowel resected	13½ yrs.
11. F. T.	65	M	Volvulus of the small bowel after ileo-colic resection	3 ft. jejunum resected	1 yr.

Four of them had 85 per cent or more of the bowel removed. As did the group with inflammatory disease and similarly extensive resections, these four had severe absorptive difficulties in the ensuing months and years. The patients with resection of one-third of the intestine suffered no serious sequelae from their resections.

Table II lists the signs and symptoms manifested by the patients. Diarrhea, the most common complaint, was noted in eight of eleven patients, the three patients who were not affected having had resections of small magnitude. Five patients lost from 23 to 50 pounds in the first three postoperative months. Patient 3 had a total weight loss of 65 pounds. This was not the result of resection but

TABLE II

General Characteristics—Symptoms and Signs

Case No.	Weakness	Weight Loss after Resection		Stools (Number per Day)	Vitamin B Complex Deficiency	Tetany	Edema	Abdominal Pain	Abdominal Distention
		lb.	time						
1. S. K.	+	50	3 mos.	7–8	+	+	+	+	+
2. D. H.	+	7	6 mos.	4–5	–	–	+	+	+
3. L. R.	+	65	6 yrs.	7	+	+	+	+	–
4. S. R.	–	0	–	7–10	–	–	+	–	–
5. P. G.	–	0	–	?	–	–	–	–	–
6. E. G.	+	35	6 mos.	20	+	–	+	–	–
7. A. S.	+	23	2 mos.	6–10	+	+		–	–
8. M. S.	+	35	2 mos.	7–10	+	–	–	–	–
9. W. B.	–	21	4 mos.	?	–	–	–	–	–
10. S. M.	–	5	1 yr.	?	–	–	–	–	–
11. F. T.	+	30	1 mo.	5–7	–	–	–	–	–

was probably due to recurrence of disease three years after resection. In addition five patients had edema of the lower extremities and showed evidence of severe vitamin B complex deficiency such as stomatitis, glossitis, cheilosis and peripheral neuritis. Three had tetany, three had frequent episodes of abdominal pain, two had moderate abdominal distention and only one showed clubbing of the fingers.

HEMATOLOGIC FINDINGS

Patients 1 through 4 had hemoglobin levels of 9 gm. per cent or less following resection (Table III). In no instance was a macrocytic anemia found. Bone marrow aspirations performed in three patients were compatible with the findings in the peripheral blood. The white blood count was normal in every instance and in the two cases in which platelets were counted they were present in adequate numbers. The prothrombin time was prolonged on one occasion and was promptly corrected by administration of vitamin K. Serum iron determinations were done in patients 1 through 4. Three had serum concentrations of 86, 51 and 33 micrograms per cent, respectively. In the presence of a normal iron binding capacity of the serum, these figures are compatible with the diagnosis of iron deficiency anemia. The fourth case had a normal serum iron. The Schilling test for vitamin B12 absorption using radioactive Co^{60} or Co^{58} was performed in three patients by Drs. Sanford Oxenhorn and Solomon Estren. Two of these were incapable of absorbing orally administered, labeled vitamin B12 while in the third, absorption was normal.

GASTROINTESTINAL STUDIES

Histamine achlorhydria was noted in one patient, while five others tested showed the presence of free hydrochloric acid in the gastric contents. Three patients had pancreatic enzyme studies performed by Dr. David Dreiling. The duodenal specimens were studied for total volume, maximum bicarbonate con-

TABLE III

Hematologic findings—gastrointestinal studies*

Case No.	Hb. (gm.%)	R. B. C.	Serum Fe μg.%	Serum IBC† μg.%	Bone Marrow	B_{12} Absorption	Prothrombin time/sec. (Control)	Gastric acidity, Units‡		Pancreatic Secretin Studies§			Roentgen Studies
								Free	Total	Vol. Ml.	Bicarb. Conc.	Amylase u./kg.	
1. S. K.	6.8	2.0	86	321		0	18 (11)	0	20	2.5	61	4.3	T. T.¶ 15 min. to right side of colon
2. D. H.	6.6	2.9	51	363	Mild granulocytic hyperplasia		13 (11)						T. T. 15 min. to transverse colon
3. L. R.	4.3	1.7	33	259						2.9	60	4.9	Diffuse inflammatory disease of almost entire small bowel—marked dilatation of colon
4. S. R.	9.0	3.6	156	320	Slight erythroid hyperplasia	Normal	14 (12)	50	70	3.6	136	6.6	T. T. 30 min. to colon; jejunum dilated
5. P. G.	13.6												
6. E. G.	12.3	4.0						45	70				T. T. 1 hr. to colostomy opening
7. A. S.	10.0	3.7			Hypocellular marrow	0	14.5 (12)	60	80				Barium in colon in 15 min.
8. M. S.	13.0	3.8						30	45				Barium in colon in 60 min.
9. W. B.	10.8	3.9					15 (12)						Barium in colon in 60 min.
10 S. M.	10.2	3.8						64	78				Barium in colon in 60 min.
11. F. T.	10.7	3.7					14 (13)						T. T. 15 min; dilatation of jejunum

* Lowest levels recorded.

† IBC = Iron binding capacity.

‡ After histamine.

§ Lower limits of normal: vol., 2.0 ml./kg.; Bicarb. conc., 90 mEq./l.; amylase 6 μ/kg.

¶ T. T. = Transit time.

centration and enzyme concentration. The total volume was normal in all three patients although two had low bicarbonate and enzyme values (Table III).

Roentgen studies of the gastrointestinal tract performed at various intervals after operation, showed rapid transit time in all patients studied. Barium administered orally appeared in the colon in 15 minutes in three patients, in 30 minutes in one, and in the remaining four, the transit time was one hour. Patient 3 was noted to have diffuse disease of the entire jejunum and ileum with multiple fistulous tracts. Marked dilatation of the bowel was noted in only two cases. Patient 6 had a well functioning colostomy and afforded the opportunity to study the effect of calcium carbonate on the transit time. A butter-rice barium meal was administered first without calcium carbonate and then with the agent added, and the length of time required for the meal to appear at the colostomy site was noted. A significant delay in the transit time was noted when calcium carbonate was added.

Five patients had roentgen studies of the skeletal system and all five showed osteoporosis and/or osteomalacia to some degree. In addition to marked decalcification, roentgen studies in patient 2 showed narrowing of the interspace between the second and third cervical vertebrae, and a chip fracture of the right hip.

CHEMICAL STUDIES OF THE SERUM

Six of eight patients tested had albumin concentrations of 3 gm. per cent or less and five of the six had reversal of the albumin globulin ratio (Table IV). Six of the eight had serum calcium concentrations below 8.5 mg. per cent; three manifested tetany during the early postoperative months. Serum alkaline phosphatase concentration was elevated in two of seven patients studied, probably due to osteomalacia. Serum cholesterol levels were low in two of five patients tested (120 and 123 mg. per cent).

TABLE IV

Chemical analyses of serum

	Serum Proteins Gm%*		Globulin	Ca mg.%*	P mg.%	Alk. Phos.† K-A u.	Cholesterol mg.%*
	Total	Albumin*					
1. S. K.	5.3	2.0	3.3	6.4	2.6	19	120
2. D. H.	6.2	2.9	3.3	7.5	2.5	16.7	
3. L. R.	3.9	2.2	1.7	8.2	2.2	9	
4. S. R.	6.4	2.3	4.1	10.6	3.1	11.1	123
5. P. G.							
6. E. G.	6.9	4.3	2.6	10.4	2.3		
7. A. S.	7.4	3	4.4	7.8	3.7	10.2	174
8. M. S.	5	4.6	2.9	8.5	3.2	7.7	180
9. W. B.							
10. S. M.							
11. F. T.	6.7	2.4	4.3	7.2	2.2	10.9	165

* Lowest levels.

† Highest levels recorded.

TABLE V

Tests of intestinal absorption

Case No.	Time After Resection	Oral Glucose Tolerance Test (100 gm. Glucose) Blood Sugar, mg.%					Vit. A Tolerance Test‡ Serum Vit. A, mg.%				Serum Carotene Level, µg.%	Fecal Fat, % Dry Wt.*†
		0	30 min.	60 min.	120 min.	180 min.	0	4 hrs	6 hrs	8 hrs		
1. S. K.	1 mon.	95	96	100	95	86	56	58	52	44	8	55.8(41.7)
	6 mos.	94	123	130	100	95	54	102	183	108	14	
	4 yrs.	86	92	96	85	74	44	44	176	120	3	
2. D. H.												+
3. L. R.	8 yrs.	98	116	102	108	113	13	15			14	56.4(20.8)
4. S. R.	17 yrs.	75	137	119	74		84	157	149	152	16	+
5. P. G.												
6. E. G.	8 mos.	80	138	116	128	60	38	95	158	158	113	42.8(36)
7. A. S.	9 mos.	102	114	90	78	85	46	31	38	34	34	19.99(15.39)
8. M. S.	7 mos.	89	120	102	88	70	87	165	154	136	56	+
9. W. B.	4 mos.	72	102	119	64	72						
10. S. M.	3 yrs.	86	120	125	68	70	87	143	332	180	117	+
11. F. T.	1 mo.	90	113	129	121	105	34	39	33	35	17	+

* Fatty acid fraction shown in parentheses.

† Plus mark indicates presence of steatorrhea on microscopic examination.

‡ 180,000 U. Vitamin A in oil.

STUDIES OF INTESTINAL ABSORPTION

All stool specimens examined microscopically showed steatorrhea; the fecal fat content consisted mainly of fatty acids with lesser amounts of soaps and neutral fats. Quantitative determinations of fecal fat were performed in four patients. Fecal fat ranged from 20 to 56.4 per cent of the dry stool weight (Table V).

Glucose tolerance tests were performed in nine patients. In only two were the curves normal. Five had flat absorption curves, while two showed evidence of impaired absorption. One of the former, patient 1, had the test repeated after receiving ACTH for several months and showed evidence of increased absorption. After discontinuation of steroid therapy, a flat curve was again obtained.

Vitamin A absorption tests were done in eight patients. In three patients the vitamin A absorption curve was flat and in five any deficiency in the ability of the bowel to absorb fat was not discernible. Three of the five patients had normal fasting serum vitamin A levels. Patient 1 had three vitamin A tolerance tests, one month, six months and four years postoperatively. The first was flat, the second and third were normal. Carotene determinations were obtained in eight patients and normal levels were found in three. These three had normal fat absorption measured by the vitamin A tolerance test.

DISCUSSION

There is a wide variation in the manner in which patients react to small bowel resection (3). There are many exceptions to the simple rule that the more extensive the resection, the more severe the intestinal "insufficiency". The condition of the remaining bowel is the most important factor in determining the postoperative fate of the patient. If disease remains or recurs in the residual bowel, the outlook may be gloomy indeed.

There are two additional factors which are perhaps not as well appreciated in determining the prognosis following resection. The first is the presence of a sufficient length of colon. Although the large bowel does not play an important role in the absorption of the three main nutrients, it acts as a reservoir and by adequate absorption of water and electrolytes, can alter the consistency of the stools. It also alters the acidity of the stools by bacterial decomposition of food. Since diarrhea is the most prominent symptom after resection, leading to weight loss, inanition, and water and electrolyte depletion, all attempts should be made to preserve the absorbing surface of the right side of the colon. This principle was used to good advantage in case 2 where jejuno-transverse colostomy had resulted in profuse diarrhea which began in the second postoperative month. In an attempt to increase the absorptive surface of the colon, the original anastomosis was replaced by one in which jejunum was anastomosed to the ascending colon, thereby adding one foot to the absorptive surface of the colon. This was effective not only in reducing the number of the stools but also in changing their consistency.

A second factor which is frequently overlooked is the psychologic status of the patient. Personality studies of patients with regional enteritis indicate that emotional factors may play a considerable role in the production and progress of the disease (4, 5). One can readily see how an undesirable sequence of events may ensue following resection for ileitis. If "psychogenic hypermotility" is present, it will not only add to the already existing impairment of absorption but may perhaps enhance the structural changes in the remaining small bowel.

With the exception of these two variables and the three factors mentioned above, the sequelae of massive resection are proportional to the magnitude of the resection. Resections of 85 per cent or more of the small bowel resulted in intestinal "insufficiency". Patients 1 and 7 had such severe nutritional disturbances that, were it not for steroid hormone therapy, they would certainly be relegated to the role of intestinal cripples. The group with 50 per cent or less of the bowel resected, exhibited no severe nutritional difficulties with the exception of patient 3. This patient had a resection of seven feet of small intestine and went into remission for three years, only to have a recurrence of the disease throughout the remaining jejunum and ileum. At present he is a poor surgical risk and his prognosis is grave.

Anemia was not an outstanding clinical feature after massive intestinal resection as reported in the literature, and when it occurred it was usually the result of some complicating factor such as diffuse carcinomatosis or the presence of a blind intestinal loop (6). In our series, anemia played a predominant role in three patients, all of whom had resections for jejuno-ileitis. There were probably numerous factors that kept the hemoglobin subnormal. Patients 1 and 2 were suspected of having recurrent disease on many occasions as a cause for the anemia, but this was never demonstrated radiographically. The patient in case 1 experienced an episode of blood loss, due perhaps to stomal jejunitis or to hypoprothrombinemia. His poor nutritional status was probably responsible for frequent non-specific, intercurrent infections combined with vitamin K deficiency. Patient 2 required monthly transfusions in addition to supportive therapy for an iron deficiency anemia first noted four years after resection. Inadequate iron absorption was assumed to be the etiologic factor. There was no evidence of hemolysis; the stools were negative for occult blood; and roentgen studies failed to show recurrent disease. The anemia in case 3 was caused by diffuse disease of the small bowel with repeated massive hemorrhages, a situation analogous to bleeding in ulcerative colitis. The possibility that his bleeding was perhaps due to the presence of a small blind loop created when resection of a portion of the jejunum was followed by side-to-side anastomosis received consideration. The anemia produced by a blind loop however, is usually macrocytic (6).

The defect in the external secretion of the pancreas is probably due to fibrosis secondary to malnutrition. Since secretin is produced almost entirely in the upper intestine, a deficiency of this hormone may result from either extensive resection or disease of the small bowel mucosa (Cases 1 and 3, respectively). The external secretion of the pancreas was further hampered by achlorhydria in patient 1. It is noteworthy that, despite a generalized deficiency of digestive secretions as indicated by achylia gastrica with diminution of pancreatic bicarbonate and amylase, the intestinal absorption of lipids in case 1 returned towards normal as indicated by the vitamin A tolerance test.

Case 1 afforded an opportunity to study the effects of severe dehydration, starvation and loss of potassium on renal function. Six months after operation, the urine was noted to contain albumin, many white cells were present in the sediment and the specific gravity was fixed at 1.010. These findings suggested the possibility of intrinsic renal disease. Further investigation led to the presumptive diagnosis of renal tubular acidosis as a result of long standing dehydration, reduction of renal blood flow, chronic hyponatremia and possible hypokalemia. The fact that the kidneys were capable of conserving sodium was good evidence that adequate renal function existed. There was evidence to suggest depressed adrenocortical function such as muscular rigidity and cramps, stiffness and hypotension.

The reaction of the feces was usually acid. Failure to secrete a normal amount of intestinal juice due to the loss of so much intestine might have led to poor neutralization of acid gastric chyme. This factor together with the presence of free fatty acids accounted for the acidity of the feces. The low pH of the feces was especially marked in patients 1 and 3, both of whom had reduced pancreatic secretions.

Microscopic examination showed the presence of large numbers of undigested meat fibers. Fat globules and fatty acid crystals could be seen along with neutral fats. In most instances the fat was hydrolyzed in the small bowel, but there was marked impairment in absorption of fatty acids. The extent of steatorrhea was striking in some patients, amounting to 56.4 per cent of the dry stool in one instance.

The outstanding nutritional difficulty after massive reaction is the absorption of fats (7–10). This has been documented by metabolic balance studies as well as other tests that measure the intestinal absorption of lipids. The use of the vitamin A tolerance test and the concentration in the serum of the vitamin A precursor, carotene, stem from our knowledge that the absorption of fat soluble vitamin A from the gut is governed by the principles that determine the intestinal absorption of fat. The desirability of using the vitamin A tolerance test instead of the time-consuming and highly technical balance studies received further impetus from the work of Legerton (11) who found a fairly regular relationship between the degree of fat absorption as determined by balance studies and the height of the vitamin A level in the serum, as determined four to six hours after a standard test dose. If the peak of a somewhat flat curve is reached at eight hours, it is indicative of retarded absorption.

The fasting level of vitamin A in the serum is of importance as well as the elevation of the serum concentration after oral intake of vitamin A in oil. The small absorbing surface readily leads to a deficiency of vitamin A as well as other vitamins, which may in turn lead to impaired intestinal absorption, thus creating a cycle in which poor intestinal absorption because of the absence of most of the intestine leads to deficiencies which further enhance absorptive difficulties.

It is almost unanimously held that there is little evidence of malabsorption of carbohydrates in cases of massive resection (9, 10), despite the flattening of the glucose tolerance curve.

Experimental evidence reveals a very definite difference in fat absorption after proximal and distal small bowel resections; increased loss of fat in the stools was noted after ileal resections (12). Protein absorption is influenced also to a greater degree by the ileal resections, although nitrogen losses in the stool were never as marked as fat losses. Only one of our patients (case 3) had a proximal bowel resection and he suffered no ill effects. The distal small bowel is involved much more often in inflammatory processes as well as in vascular accidents, accounting perhaps for the nutritional disturbances seen after massive resections.

The presence of an intact ileocecal valve is of great importance following extensive resection, particularly if it involves the distal small bowel. Patient 4 had 50 per cent of the distal small bowel resected and, except for diarrhea which has not been incapacitating, has shown little if any evidence of malabsorption. Since the ileocecal valve was not resected, it continued its function of delaying the rapid passage of food into the colon thus assuring greater absorption in the ileum.

GENETIC ASPECTS

Familial occurrence of regional enteritis and enterocolitis has been well documented (13). There have been a considerable number of reports of the disease occurring in close blood relatives, e.g., in three siblings, in mother and daughter, or in father and son (14, 15). The family history of patient 1 is noteworthy, since four close blood relatives were found to have this disease. The mother of the patient showed definite involvement of the terminal ileum roentgenologically. Two younger brothers had the diagnosis confirmed at operation; one of them had an ileotransverse colostomy for regional ileitis and ulcerative colitis. The other had a partial jejunectomy for diffuse disease of jejunum and ileum. The recognition that familial occurrence is not rare in regional ileitis may provide a possible clue to the etiology of the disease. In comparison to idiopathic ulcerative colitis, where the presence of more than one case in the same family is unusual (16), the contrast is striking and perhaps difficult to accept as mere coincidence. One may speculate that the low familial incidence of ulcerative colitis probably excludes contagion and heredity as important factors in the genesis of this disease. In jejuno-ileitis on the other hand, the possibility may be considered that genetic transmission and/or infectious agents are important in the evolution of the disease.

MALABSORPTION SYNDROME FOLLOWING GASTRO-ILEOSTOMY

Gastro-ileostomy is a rare surgical error. The first case was reported in 1915 (17) and by 1947 a total of 27 cases had appeared in the literature (18). In every instance gastro-jejunostomy for peptic ulcer was the intended operative procedure. Analysis of the symptomatology in the 27 cases revealed weight loss in 19, abdominal pain in 17, diarrhea in 14, vomiting in 6, ileal ulcers in 6, and hemorrhage in 3. The first reported case of gastro-ileostomy following subtotal gastrectomy appeared in 1951 (19). Symptoms caused by inadvertent gastro-ileostomy following subtotal gastrectomy appear sooner in the postoperative period than following a gastro-enterostomy without resection. When gastro-enterostomy is performed for duodenal ulcer, despite the anastomosis of the stomach to the ileum instead of jejunum, a patent pylorus is preserved, thus assuring the passage of some of the food into the jejunum and increasing the quantity of food absorbed. Following subtotal gastrectomy, if the ileum is anastomosed to the stomach, particularly if lower ileum is selected, unabsorbed food enters the colon rapidly and, since the pylorus has been resected, there is no avenue of escape for absorption of any nutrients. Steatorrhea and other features of the malabsorption syndrome soon appear. Until the mistake is identified and corrected, the sequelae are exactly the same as those following massive resection.

One possible clue to the diagnosis of gastro-ileostomy in a patient manifesting diarrhea and weight loss after a subtotal gastrectomy is the presence of a flat glucose tolerance curve. The occurrence of a flat curve was noted in a previously reported instance of gastro-ileostomy (20) and in patient 12 led us to suspect the correct diagnosis before roentgen studies were performed. In a patient with a properly performed Billroth II operation, the oral glucose tolerance curve is normally characterized by an early peak followed by a sharp drop to hypoglycemic levels (21). In contrast, the finding of impaired intestinal absorption of glucose should make one suspect gastro-ileostomy.

ANALYSIS OF VARIOUS THERAPEUTIC REGIMENS

Dietary Measures. The diet should include a liberal quantity of carbohydrate since this nutrient is well absorbed. Some starches causing fermentation and abdominal distention should be avoided. The protein intake should be moderate to high. Fat is poorly tolerated and patients will voluntarily restrict this foodstuff to a minimum. Resection of the small bowel leads to a low calorie intake thus depressing the basal metabolic rate. Reduction in caloric and other metabolic requirements is an important compensatory factor in keeping patients who have had massive resections alive. Our patients did not care for pureed foods and did better on whole foods. Similar observations have been made by other investigators (10). A plausible explanation for this perhaps is that foods enjoyed by the patient stimulate a greater flow of digestive ferments. One must never overload the bowel to the point of fatigue, however.

Supportive Therapy. Calcium should be administered routinely following extensive small bowel resection. When hypocalcemia exists the parenteral as well as the oral route should be utilized until normal calcium balance is restored. Iron deficiency should be corrected by the use of ferrous salts. It is understandable that oral iron medication is often ineffective after massive resection in treatment of iron deficiency anemia, whereas adequate doses given parenterally are apt to produce dramatic results. The parenteral preparation most extensively used is saccharated oxide of iron which must be administered intravenously. Recently, a new iron-dextran complex which can be given intramuscularly has been shown to be similarly effective in hemoglobin regeneration (22). This can be given in large doses and increases the safety of parenteral therapy. If megaloblastic anemia is present, vitamin B12, liver extract, and/or folic acid therapy is indicated. In presence of marked hypoalbuminemia, daily infusions of salt-free albumin combined with high protein intake proved to be of great benefit in our experience. Keeping the blood count normal and maintaining a normal level of plasma protein will undoubtedly assist in improving the absorption of important elements through the intestinal mucosa. Many patients exhibit multiple vitamin deficiencies while diarrhea and steatorrhea are active. Evidence of deficiency of factors of the vitamin B complex is most common, but evidence of the lack of vitamins A, D, E and K as well as of ascorbic acid, may be present. Thus therapy should include multivitamin preparations. Hemorrhagic manifestations caused by hypoprothrombinemia usually respond well to adequate parenteral vitamin K therapy. Occasionally, even massive doses of vitamin K fail to raise the serum prothrombin level, necessitating multiple blood transfusions.

Steroid Therapy. Much evidence has been accumulated to show that adrenocortical hormones exert an effect on intestinal absorption of fat and fat-soluble vitamins. Adlersberg and co-workers noted clinical improvement manifested by increased sense of well-being, improved appetite, disapperance of diarrhea and weight gain in patients with idiopathic sprue who had been refractory to other forms of therapy (23). Absorption studies following the use of steroids in sprue patients showed a diminution in fecal fat excretion and increased in serum vitamin A level, although the vitamin A tolerance curve did not change much. Other investigators, on the other hand, found that the fecal excretion of fat sometimes increased during the treatment with hormones, and the flat vitamin A tolerance curve characteristic of sprue was markedly raised during the administration of ACTH (24). These paradoxical observations were explained by a dual effect of the hormone producing increased intestinal absorption as well as an increased enteric excretion of endogenous fat (26).

The steroids were used in two of our patients for the purpose of improving intestinal absorption with gratifying results. Patient 1 presented a serious nutritional problem until ACTH was started three months after resection. Prior to the use of corticosteroid therapy he had to be readmitted on two occasions because of starvation, dehydration and inanition. During his third postoperative admission, ACTH, 80 mg. daily, was administered by intravenous drip. This produced a ravenous appetite. His strength improved and he gained seven pounds in two weeks. After discharge, he remained on a small daily maintenance dose of steroid hormone. When he was again admitted three months later because of hypocalcemic tetany, his vitamin A and glucose tolerance tests, which were flat shortly after operation, now indicated markedly improved intestinal absorption. When steroid therapy was discontinued, his glucose tolerance test again became flat. He was started on prednisone (15 mg. daily) in March 1955 and in the ensuing year gained 20 pounds. His stools are formed, he feels better than he did since resection and believes that he is ready for gainful employment.

Patient 6, like patient 1, was left with only 18 inches of small bowel. After surviving her resection and postoperative cholecystectomy, she returned to the hospital because of diarrhea, weight loss and tetany, all of which were referable to the disturbances caused by the extensive resection. She was treated with cortisone, and within four days her weight improved and diarrhea subsided. She had not had any significant difficulty since, receiving a maintenance dose of prednisone in addition to vitamins.

Studies on the role of the adrenal cortex in intestinal absorption have thus far been inconclusive. Adrenocortical hypofunction has been suggested as the cause of steatorrhea (25), but no abnormalities have been noted in the adrenal glands in patients with sprue. Many patients with Addison's disease have diminished intestinal absorption, however (26). Whatever the underlying mechanism may be, the improved since of well-being and cheerful mental outlook which happens to most patients receiving steroid for any condition and the enormously increased appetite with resultant improvement in nutrition are beneficial effects which are particularly desirable after massive bowel resection. The improved emotional state may be helpful to these patients who are often depressed. The mere fact that marked improvement in diarrhea and sense of well-being can occur so promptly with a new drug after all other forms of therapy are unavailing may give hope and optimism to a discouraged patient and thus act as a crutch providing a sense of security.

Complications attending the therapeutic use of corticotropin and the cortisones over a prolonged period must be guarded against. The detection and management of acute infections in patients receiving steroid therapy is a challenging clinical problem. The low resistance to infections and stress of patients who have had extensive resections is well known. In addition, the manifestations of infection may be masked by corticosteroid therapy. Therefore, full attention should be given to minor symptoms and signs of infection.

The negative calcium and/or nitrogen balance associated with steroid therapy may result in intensification of the pre-existing osteomalacia or osteoporosis. Multiple fractures including compression fractures of the vertebrae may occur. The refractory iron deficiency anemia (patient 2) might be aided by corticosteroid therapy, but, in view of the marked changes already present in her skeletal system, one would hesitate before beginning this therapy.

IS MASSIVE RESECTION FOR JEJUNO-ILEITIS WARRANTED?

The course of jejuno-ileitis is variable. It may be very mild with little tendency to fever, weight loss or other general systemic manifestations. On the other hand, severe forms of the disease may produce general toxemia, marked weight loss and loss of appetite. The inflammatory changes in the intestine interfere with the absorption in the involved loops and the irritating effect of the disease on the entire gastrointestinal tract produces hypermotility and further impairment of absorption. Arrest of the disease may be achieved in certain cases of ileitis after resection. However, there is a distressingly large group of patients who have lost a large part of intestine through resection and then have further activity of the disease with disturbance of the function of the remaining bowel. A recurrence rate as high as 34 per cent has been reported; most of the recurrences occurred within two years after resection (27). The question of serious nutritional difficulties has frequently been a factor limiting the extent of resection. Kiefer (27) stressed the importance of secondary, tertiary and even fourth resections in the aggressive attempt to eradicate disease. One-third of his patients, subjected to secondary operations, had relief of ileitis but at the expense of the nutritional status. The severe absorption defects resulted in "intestinal invalidism" in some. Numerous resections or one massive resection which leaves the patient a nutritional cripple can hardly be considered a cure of the disease. Cattell (28) suggested a planned multiple stage procedure of intestinal resection on the basis that patients can be maintained in a better nutritional status. An alternative procedure is jejuno- or ileo-colostomy with exclusion of the diseased bowel followed by resection six months later if necessary.

Experience seems to indicate that surgical intervention should be confined to those cases complicated by obstruction, abscesses or fistulas and those in which a most thorough medical regimen has failed. When an indication for surgery arises the less radical procedure of side tracking and exclusion is probably the operation of choice. The mortality and recurrence rates are lower than after extensive resection (29). The side tracking operation frequently obviates the need for future resection by excluding the diseased bowel from the fecal streams. The inflammatory process usually subsides when the bowel is put to rest. If the excluded bowel fails to heal, or disease recurs and medical therapy does not halt the progress of the disease, massive resection is warranted and is facilitated by the fact that a large portion of the bowel has not been functioning for months preceding resection.

After extensive resection the ability of the bowel to absorb fats is impaired to a greater extent than absorption of the other nutrients. In addition, lipids are the last of the food substances to show improved absorption, as measured by vitamin A tolerance and balance tests, after resection. The ability of corticotropin and the cortisones to improve absorption of lipids has been well documented (30) and unless a strong contra-indication is present these hormones may be administered in the early postoperative period, as soon as steatorrhea becomes evident, as well as later along with dietary and replacement therapy. Steroid hormones also seem to promote absorption of carbohydrates, calcium, vitamin K and hemopoietic substances (31).

SUMMARY

1. Eleven cases of extensive resection of the small intestine are presented. Five of the resections were for jejuno-ileitis, the remainder for acute vascular conditions necessitating emergency resection.

2. Nine patients have been under observation for periods varying from two to 13½ years, one was lost to follow-up after two years and one died.

3. Diarrhea, steatorrhea, weakness and considerable weight loss were the postoperative sequelae encountered most often. Other frequent findings were abdominal pain, tetany, edema, osteoporosis, anemia, hypoproteinemia, hypocalcemia, low serum vitamin A and carotene levels, and flat glucose and vitamin A tolerance curves.

4. Despite numerous variable factors, the most important of which is the status of the remaining bowel, the severity of the sequelae is proportional to the magnitude of the resection.

5. ACTH and the cortisones have a beneficial effect on intestinal absorption and should be used when malabsorption appears in the early postoperative period and later, if necessary.

6. A case report of a patient on whom an inadvertent gastro-ileostomy was performed is presented and the results of exclusion of almost the entire small bowel is discussed. The oral glucose tolerance test may prove useful in differentiating between gastro-ileostomy and gastro-jejunostomy when diarrhea and weight loss persist after subtotal gastric resection.

REFERENCES

1. Flint, J. M.: The Effect of Extensive Resection of the Small Intestine. Bull. Johns Hopkins Hosp., 23: 127, 1912.
2. Berman, I. G., Ulevitch, H., Haft, H. H., and Lemish, S.: Metabolic Studies of an Unusual Case of Survival following Resection of All but 18 Inches of Small Intestine. Ann. Surg., 132: 64, 1950.
3. Weckesser, E. C., Chinn, A. B., Scott, M. W., and Price, J. W.: Extensive Resection of Small Intestine. Am. J. Surg., 78: 706, 1949.
4. Stewart, W. A.: Psychosomatic Aspects of Regional Ileitis. N. Y. State J. Med., 49: 2820, 1949.
5. Grace, W. J.: Life Stress and Regional Enteritis. Gastroenterology, 23: 542, 1953.
6. Jackson, W. P. V., and Linder, G. C.: Small Gut Insufficiency following Intestinal Surgery. South African J. Clin. Sc., 2: 205, 1951.

7. Althausen, T. J., Doig, R. K., Uyeyama, K., and Weiden, S.: Digestion and Absorption after Massive Resection of the Small Intestine. Gastroenterology, 16: 126, 1950.
8. West, E. S., Montague, J. R., and Judy, F. R.: Digestion and Absorption in a Man with Three Feet of Small Intestine. Am. J. Digest. Dis., 5: 690, 1938.
9. Todd, W. R., Dittebrandt, M., Montague, J. R., and West, E. S.: Digestion and Absorption in a Man with All but Three Feet of Small Intestine Removed Surgically. Am. J. Digest. Dis., 7: 295, 1940.
10. Jackson, W. P. V., Linder, G. C., and Berman, S.: Small Gut Insufficiency following Intestinal Surgery. South African J. Clin. Sc., 2: 70, 1951.
11. Legerton, C. W. J., Texter, C. E., and Ruffin, J. M.: Observation on the Vitamin A Tolerance Test as an Index of Degree of Fat Absorption. Gastroenterology, 23: 447, 1953.
12. Kremen, A. J., Linner, J. H., and Nelson, C. H.: An Experimental Evaluation of the Nutritional Importance of Proximal and Distal Small Intestine. Ann. Surg., 140: 439, 1954.
13. Metzger, H. N., and Frobese, A. S.: Terminal Ileitis in a 15-year-old Boy and in the Mother 19 Years Previously. Gastroenterology, 31: 439, 1956.
14. Brown, P. W., and Scheifley, C. H.: Chronic Regional Enteritis Occurring in Three Siblings. Am. J. Digest. Dis., 6: 257, 1939.
15. Kirsner, J. B., Owens, F. M., Jr., and Humphreys, E. M.: Regional Enteritis in Father and Son. Gastroenterology, 10: 883, 1948.
16. Jackman, R. J., and Bargen, J. A.: Familial Occurrence of Chronic Ulcerative Colitis. Am. J. Digest. Dis., 9: 147, 1942.
17. Martin, F., and Carroll, A. H.: The Role of Gastroenterostomy in the Treatment of Ulcers. Ann. Surg., 61: 567, 1915.
18. Brown, C. H., Colvert, J. R., and Brush, R. E.: Gastroileostomy, a Rare Surgical Error. Gastroenterology, 8: 70, 1947.
19. Windwer, C., and Farber, D.: Gastroileostomy following Subtotal Gastrectomy. Rev. Gastroent., 17: 1040, 1951.
20. Cropper, C. F. J., and Haughton, P. W.: Ileo-jejunal Insufficiency Arising from Faulty Anastomosis. Lancet, 2: 439, 1950.
21. Adlersberg, D., and Hammerschlag, E.: Mechanism of the Post-gastrectomy Syndrome. J.A.M.A, 139: 429, 1949.
22. Coppell, D. F., Hutchinson, H. E., Hendry, E. B., and Conway, H. A.: A New Carbohydrate Iron Hematinic for Intramuscular Use. Brit. Med. J., 2: 1225, 1954.
23. Adlersberg, D., Colcher, H., and Drachman, S. K.: Effects of Cortisone and Pituitary ACTH in the Sprue Syndrome. Gastroenterology, 19: 674, 1951.
24. Taylor, H. B., Comfort, M. W., Wollaeger, E. F., and Power, M. H.: The Effect of Cortisone on Non-Tropical Sprue (Idiopathic Steatorrhea). J. Clin. Invest., 30: 678, 1951.
25. Verzar, F., and McDougall, E. J.: Absorption from the Intestine. London, Longmans, Green and Company, 1936. p. 181.
26. Thorn, G. W., Forsham, P. H., Framley, T. F., Hill, Jr., S. R., Roche, M., Staehlin, D., and Wilson, D. L. The Clinical Usefulness of ACTH and Cortisone. New Eng. J. Med., 242: 865, 1950.
27. Kiefer, E. D.: Recurrent Regional Ileitis. Lahey Clin. Bull., 8: 149, 1953.
28. Cattell, R. B.: Massive Resection of Small Intestine. Lahey Clin. Bull., 4: 167, 1945.
29. Ginsberg, L., and Garlock, J. H.: Regional Ileitis. Ann. Surg., 116: 906, 1942.
30. Colcher, H., Drachman, S. R., and Adlersberg, D.: Management of Intractable Sprue with Cortisone and Adrenocortropin (ACTH). Ann. Int. Med., 38: 554, 1953.
31. Badenoch, J. D.: Cortisone in Idiopathic Steatorrhea. Brit. Med. J., 1: 356, 1952.

INDEX

Absorption, fat, after massive resection of small intestine, 244
Absorption, intestinal, physiology of, 7–25
ACTH, *see* Corticotropin
Active transport process, in fat absorption, 8
Adrenal cortex, in active fat transport, regulatory function of, 12
Adrenocortical steroids
  fatalities after, 220–221
  after massive resection of small intestine, 246–248
  in malabsorption syndrome, 213
  in osteoporosis, etiologic role of, 186
  see also Corticosteroid therapy; Corticotropin; Cortisone
Agammaglobulinemia, spruelike syndrome in, 33
Amino acids
  absorption, selective, 21–22
    demonstration of by preferential absorption of *L*-isomer, 21
  and protein absorption, 20–22
Anemia
  hypochromic, in malabsorption syndrome, 154. *See also* Iron
  macrocytic, 154
    in tropical sprue, 130–132
    vitamin B_{12} for, 170
  pernicious, in idiopathic sprue, 130–131, 133–134
    "intermediate" erythropoiesis in, 135
    and vitamin B_{12}, 59–65, 137
Appendicitis, acute, in sprue syndrome, 78–79
Asthenia, in malabsorption syndrome, 56

Barium column, segmented in small intestine, 193–195, 202–203
Bile salts, in fat absorption, hepatic secretion necessary for, 10
Blood, in malabsorption syndrome
  in idiopathic sprue, 130–139
  leukocytes, qualitative changes in, 136
Blood chemical studies, in malabsorption syndrome, 119–120
Bone, *see* Osseous changes
Bone marrow, in idiopathic sprue, 130–139

Calcium
  intestinal absorption of, 14
  serum, parathyroid response to lowering of, 184
  transport, favoring of by protein, 14
  see also Osseous changes
Carbohydrates, absorption of, 15–20. *See also specific substances*
Carotene, serum, absorption of, 40–43
Celiac disease, in childhood, 110, 157, 162
Cholesterol, dietary, lymphatic transportation of, 13
Cholesterol, serum, in active sprue, 37–40
Clinical aspects of malabsorption syndrome, 32–45, 112–127
Corticosteroid therapy, effects of on gastrointestinal manifestations of malabsorption syndrome, 169–170
Corticosteroids, *see* Adrenocortical steroids
Corticotropin (ACTH), in malabsorption syndrome, 170, 213, 247
  and glucose absorption, 17
  and osteomalacia, 179–180
Cortisone, for adult malabsorption syndrome, 162

Diet
  gluten-free, in malabsorption syndrome, 208
  after resection of small intestine, 245–246
Dietary management, in malabsorption syndrome, 206–222

Edema, in idiopathic sprue, 34–36, 43
Electrolytes
  depletion of in steatorrhea, 47–56
  transfer of, necessity of for water absorption, 22–23
Enteritis, regional
  genetic aspects of, 242
  psychologic status of patient in, 242
Erythropoiesis, "intermediate," in atypical pernicious anemia, 135

Fat
  absorption, 10–15
    after massive resection of small intestine, 244
    hepatic secretion of bile salts necessary for, 10
    pancreatic secretion of lipase necessary for, 10
    transport process in, 8
  synthesis, neutral, inhibition of by phlorhizin, 11, 13, 22
  transport, adrenal cortex regulating, 12
  vitamin K causing malabsorption of, 17
Fatty acids, absorption of, 11
Folic acid, malabsorption of in sprue syndrome, 138
Fructose, selective absorption of, 18, 19–20

Galactose, selective absorption of, 18
Gastrectomy, subtotal, malabsorption after, 200
Gastro-ileostomy, malabsorption syndrome after, 245
Glucose, selective absorption of, 18
  and ACTH, 17
Glycerol, absorption of, 10–11

Hemorrhagic manifestations, in idiopathic sprue, 143–155
Hyperparathyroidism, in sprue, 184–185
Hypocalcemia, in idiopathic sprue, 154
Hypoproteinemia
  intractable, in idiopathic sprue, 34–36, 43, 44
  in sprue, 138
Hypoprothrombinemia, *see* Vitamin K

Infections, masked, in steroid therapy, 222
Intestine, small
  biopsy by oral route, 99–111
  fat absorption after massive resection of, 244
  mucosal atrophy of, in idiopathic sprue, 104–109, 110
  resection of, 225–249
    in jejeuno-ileitis, 225, 230–232, 236
  roentgenologic appearance of after therapy, 196–198

  segmented barium column in, 193–195, 202–203
  in sprue
    dilatation of lumen in, 191–193, 203
    pathologic alterations in, 90, 97

Iron
  absorption of, 24–25
  -deficient anemia, in nonceliac sprue, 134
  and hypochromic anemia, 154
  malabsorption of, 138
  therapy, indications for in microcytic hypochromic anemia, 210

Jejeunal biopsies, 94–95, 99
Jejeuno-ileitis
  and malabsorption syndrome, 72–74, 248
  resection of small intestine in, 225, 230–232, 236

L-isomer, in selective amino acid absorption, preferential absorption of, 21
Leukocytes, *see* Blood
Leukopenia, in sprue, 135
Lipase, for fat absorption, necessity of pancreatic secretion of, 10
Lipid metabolism, disturbances in, in sprue syndrome, 32–45
Lipids, total, determination of in active sprue, 37–40
Liver
  extract, parenteral administration of, 208
  pathologic role of in sprue syndrome, 91
Lymphosarcoma, and secondary sprue, 198–199

Macrocytosis, in tropical sprue, 130–132
Myeloradiculoneuropathy (pseudotabes), in malabsorption syndrome, 168–169

Neurologic manifestations, in malabsorption syndrome, 157–170
Neuropathy, in malabsorption syndrome, 55–56

Osseous changes, in malabsorption syndrome, 172–186
Osteomalacia
  and ACTH, 179–180
  in malabsorption syndrome, 172–181, 183
  in sprue, 154
Osteoporosis, in malabsorption syndrome, 165, 172–181, 183

Pancreas
  in malabsorption syndrome, 199
  pathologic role of in sprue syndrome, 90
  pancreatic secretion, role of in idiopathic sprue, 69–75
  pancreatitis, chronic, 74–75
Parathyroid gland, response of to serum calcium lowering, 184
Pathologic studies, in idiopathic sprue, 77–97
Phlorhizin, inhibition of neutral fat synthesis by high concentrations of, 11, 13, 22
Phospholipid determinations, in active sprue, 37–40
Phosphorylation
  and absorption, 11
  theory of selective absorption, 18–19, 22
Pitressin, increase in water absorption produced by, 22
Potassium, depletion of in steatorrhea, 47–56
Prednisone, *see* Corticosteroids
Protein
  absorption, 20–22. *See also* Amino acids
  calcium transport favored by, 14
  metabolism, disturbances in, in sprue syndrome, 32–45
Psychologic status of patient in regional enteritis, 242
Pyelonephritis, in sprue syndrome, 81–82

Roentgenology
  examination, 120–121
  in malabsorption syndrome, 188–204
  of small intestine, after therapy, 196–198

Schilling test for urinary excretion, 62–63
Secretin test, 69–75
Segmentation of barium column in small intestine, 193–195, 202–203
Steroids, *see* Adrenocortical steroids
Syphilis, and malabsorption syndrome, 163, 165, 169

Testosterone, and malabsorption syndrome, 186
Tetany
  calcium lactate or calcium gluconate for, 147
  in severe sprue syndrome, 56, 79–80, 165–167
Tracheo-bronchitis, in sprue syndrome, 82–83

Ulcer, peptic, in malabsorption syndrome, 73–74
Ulcerative colitis, in malabsorption syndrome, 72–74

Vitamin A, impaired absorption of, 40–43, 44
Vitamin B_{12}
  absorption of in pernicious anemia, 59–65
  deficiency of in pernicious anemia, 137
  intestinal uptake of in malabsorption syndrome, 58–66
  for macrocytic anemia, 170
  malabsorption of, 137–139
  for malabsorption syndrome, 157–160, 208
  radioactive, 62–64
Vitamin D, increase of calcium absorption by, 15
Vitamin K
  deficiency
    in hypoprothrombinemia, 143, 152
    in sprue, 154
  relation of to malabsorption of fat, 17
  therapy, 148–150

Water
  absorption, 22–24
    electrolyte transfer necessary for, 22–23
    increase in by Pitressin, 22
  excretion, in steatorrhea, 47–56
Weight, loss of, in malabsorption syndrome, 54–55
Whipple's disease, and secondary sprue, 199

CENTRAL FOOD TECHNOLOGICAL RESEARCH INSTITUTE, * MYSORE. *
LIBRARY

checked by 29/8/5

1.10.80

21/11/89

5-5-97

CHECKED 2008

VERIFIED 2013

CFTRI-MYSORE
3923
Malabsorption sy..